

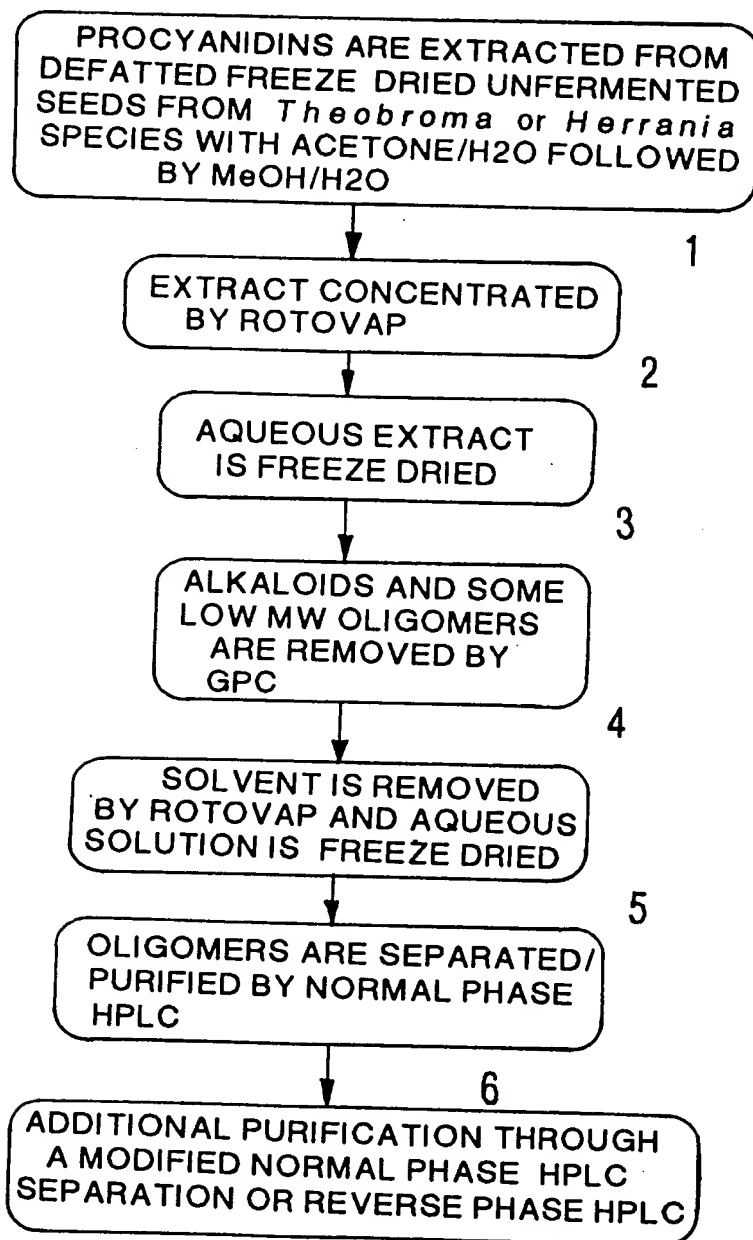
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FIG.1

Summary of the current purification protocol

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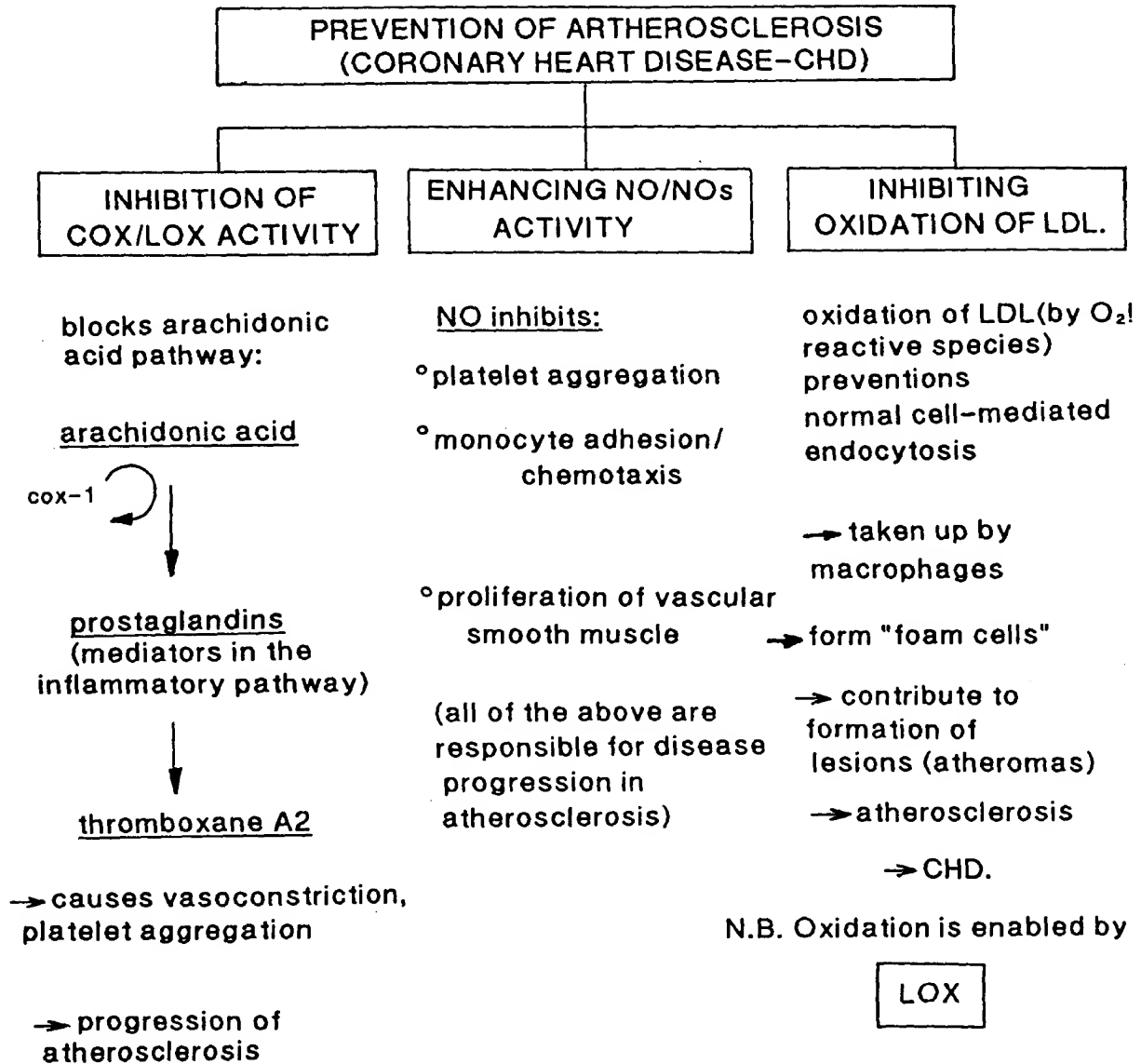
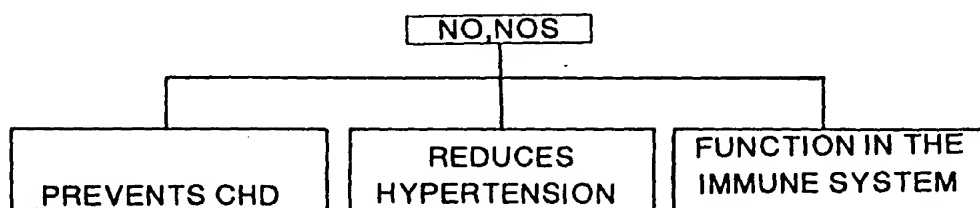


Chart showing the major contributing factors in the progression of Coronary Heart Disease (CHD) and how the activity of cocoa procyanidins contributes to the prevention of the progression of the disease state

FIG.2



The cocoa procyanidins induce the activity of NOS and therefore the resulting production NO, thereby enhancing the health benefits mediated by the activity of nitric oxide (NO).



°inhibits platelet aggregation, monocyte adhesion, chemotaxis and vascular smooth muscle proliferation thereby causing vascular relaxation and preventing the disease progression of CHD.

By lowering blood pressure via the following mechanism:

vascular endothelial cells release eNOS

→result in production of NO

→NO relaxes vascular smooth muscles, increasing vascular lumen diameter

→ lowers blood pressure

→ induces hypotension.

° Macropages have a different NOS(iNOS)

° iNOS gene transcription is controlled by cytokines

° iNOS activity results in macrophage NO production at sufficient concentrations to inhibit ribonuclease reductase

→causes inhibition of DNA synthesis

→potential mechanism of action in anti-tumor and anti-microbial function.

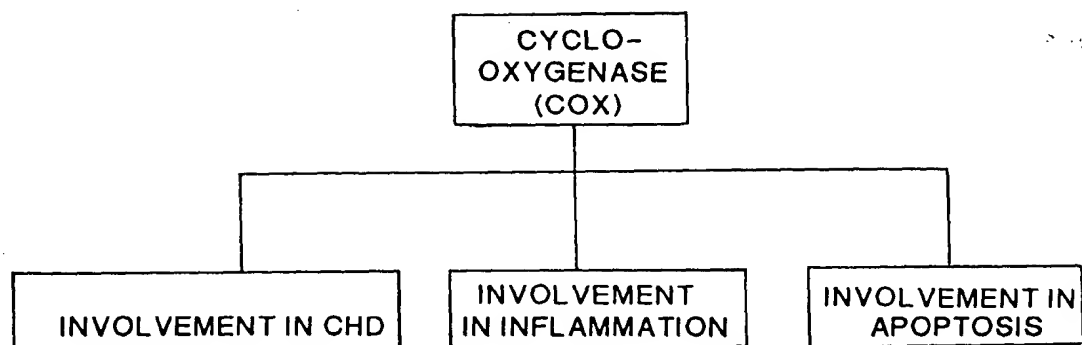
HYPERTENSION RESPONSIBLE FOR CARDIOVASCULAR DISEASES:

including:

stroke
heart attack
heart failure
kidney failure

FIG.2b

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COX-1 is essential in the arachidonic acid pathway which results in the production of thromboxane.

→ thromboxane and prostaglandins which promote platelet aggregation and vasoconstriction

→ resulting in progression of atherosclerosis.

COX-1 is an essential enzyme in the inflammatory pathway, the penultimate products of which (the prostaglandins) are largely responsible for the inflammatory pathway, the results of which contribute to a variety of diseases including:

→ bowel disease, arthritis, edema, gingivitis/periodontitis, etc.

COX-2 producing cells lines show enhanced expression of genes known to be involved in apoptosis:

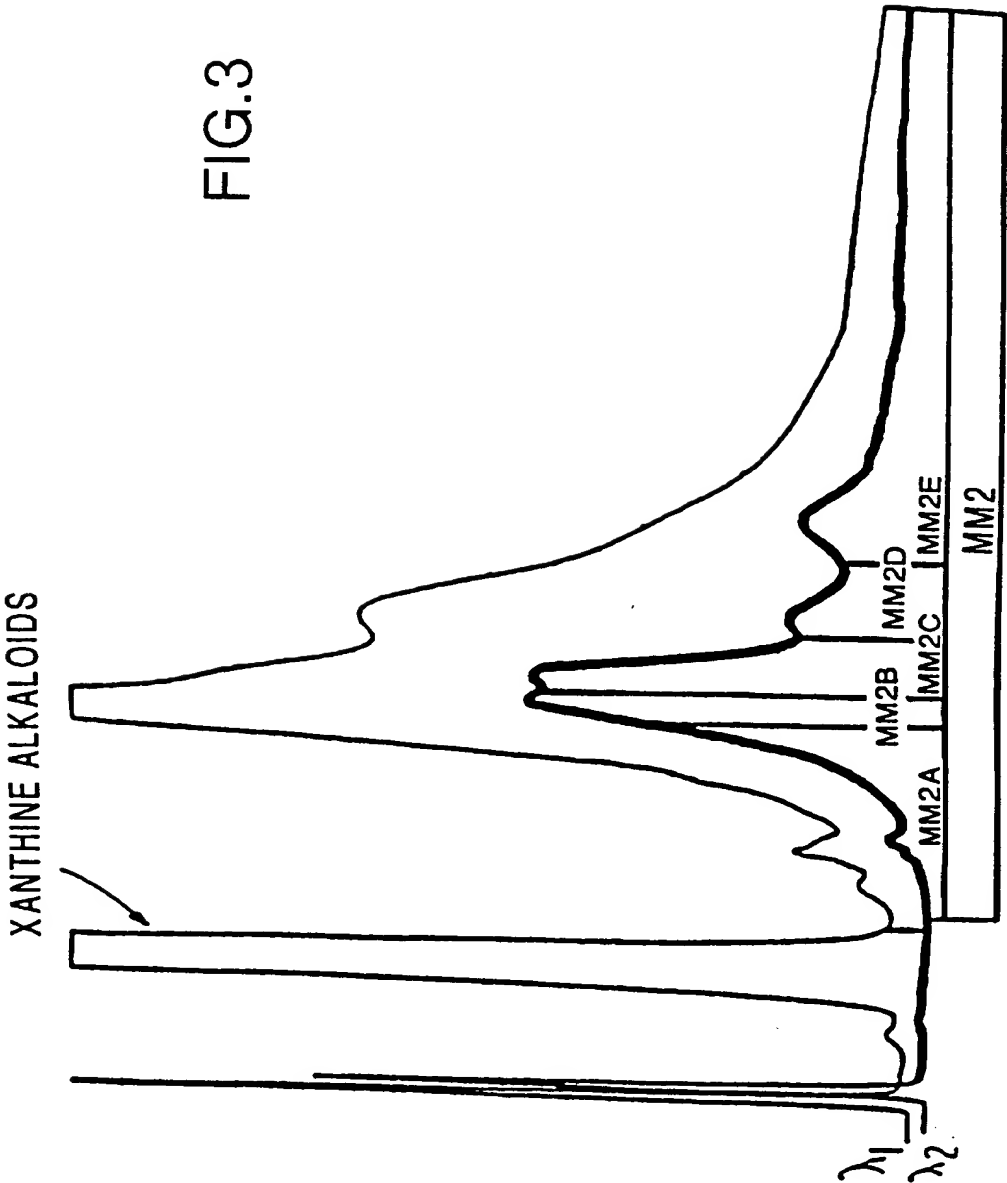
→ potential putative mechanism of killing tumor cells.

The cocoa procyanidins inhibit the production of cyclo-oxygenase, thereby blocking the arachidonic acid pathway, which is responsible for the inflammatory response and the vasoconstrictive and platelet aggregating responses which contribute to the disease progression of CHD.

FIG.2c

APPROVE	C.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

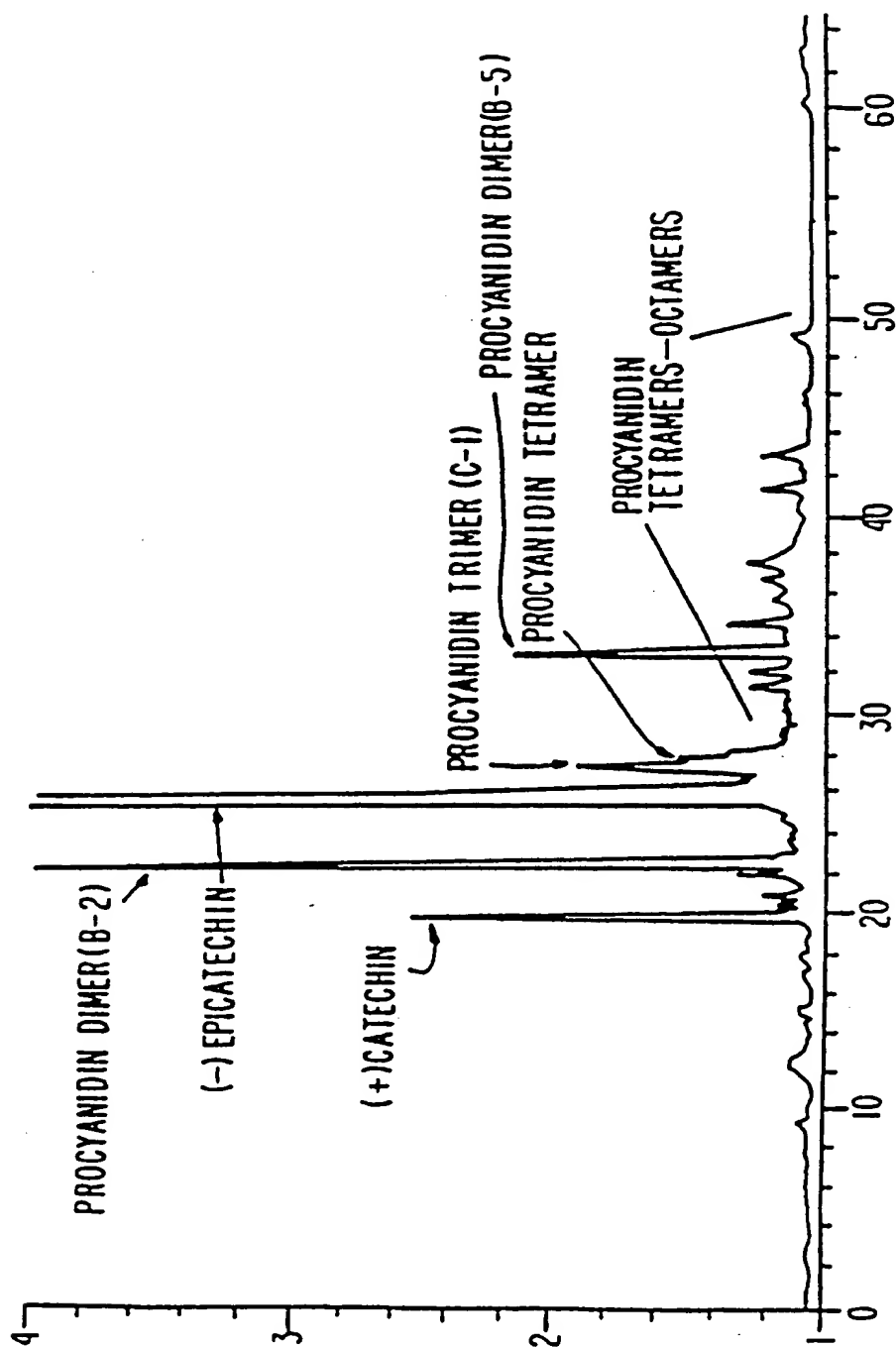
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FIG.4

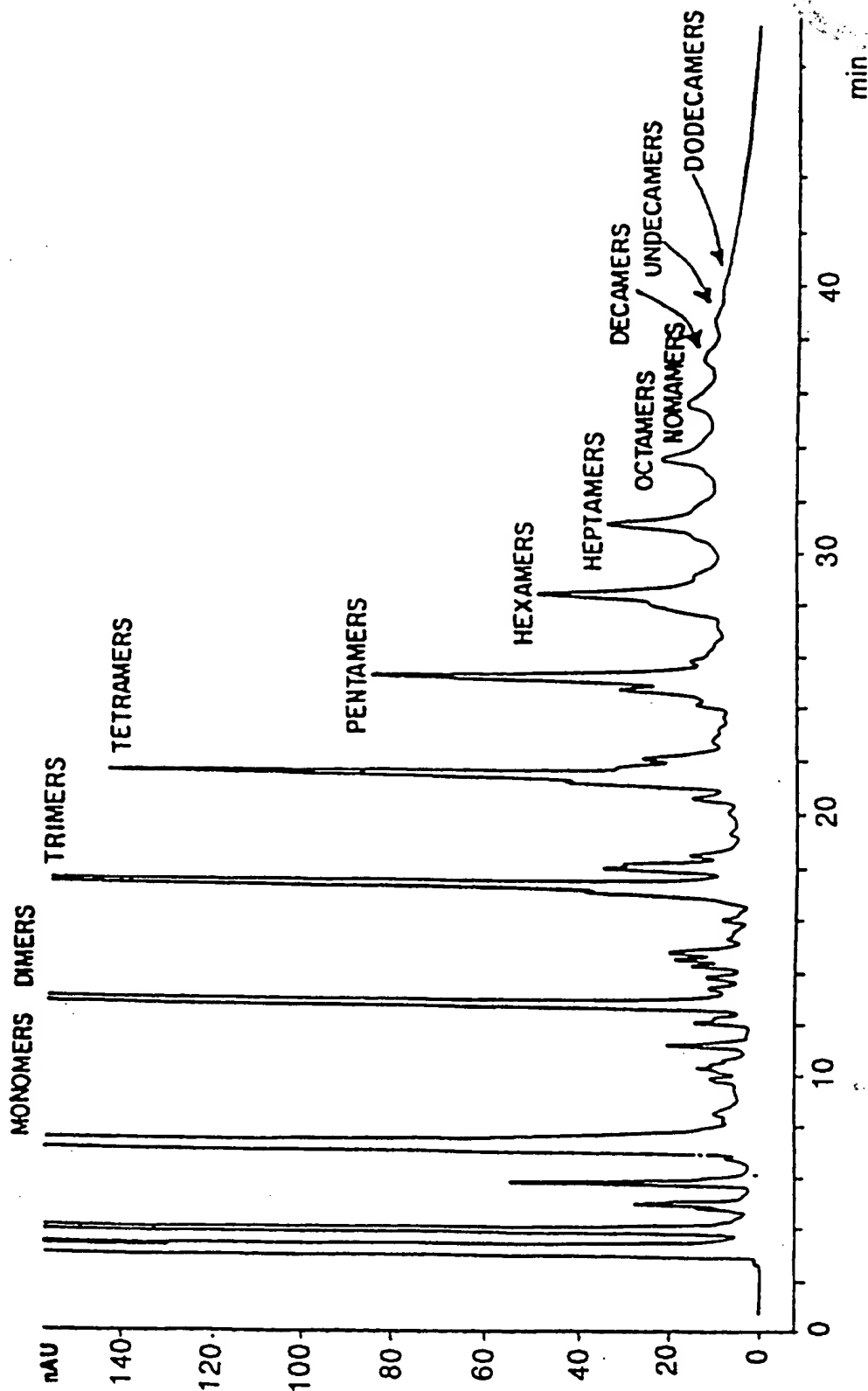


APPROVED	C.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

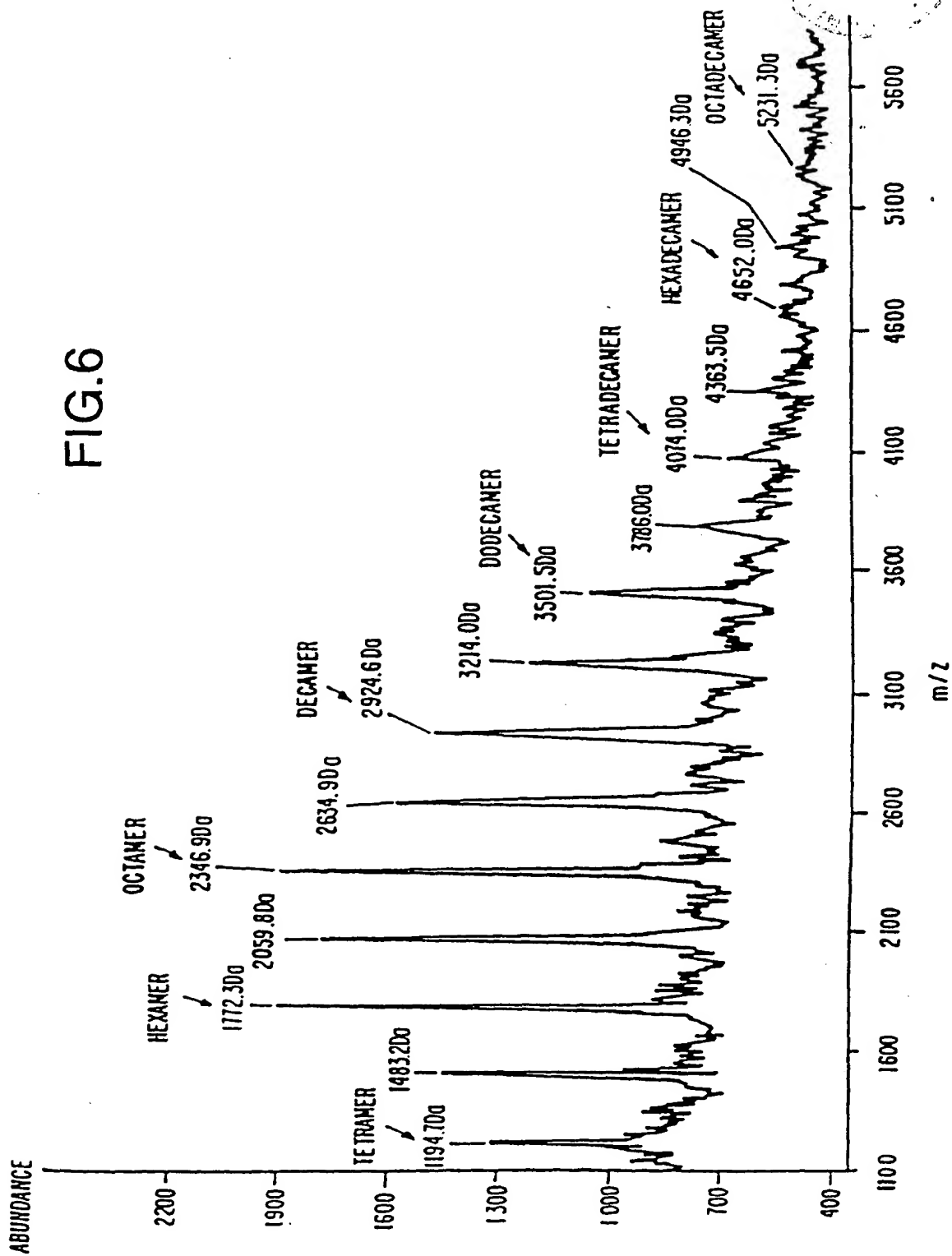
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FIG.5

DADI A, Sig=280, 4 Ref=580, 40 of 4078/009-0401.D



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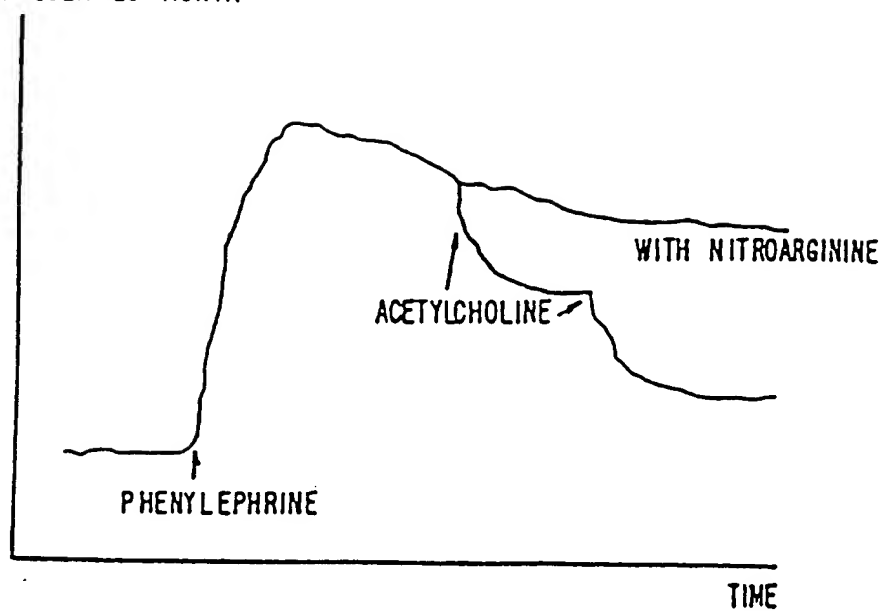
APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
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FIG.7

CONTRACTION OF ISOLATED AORTA



APPROVED	C.G. FIG.	
BY	CLASS	SUBCLASS
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FIG.8A

EFFECT OF COCOA PROCYANIDIN FRACTION A ON
BLOOD PRESSURE

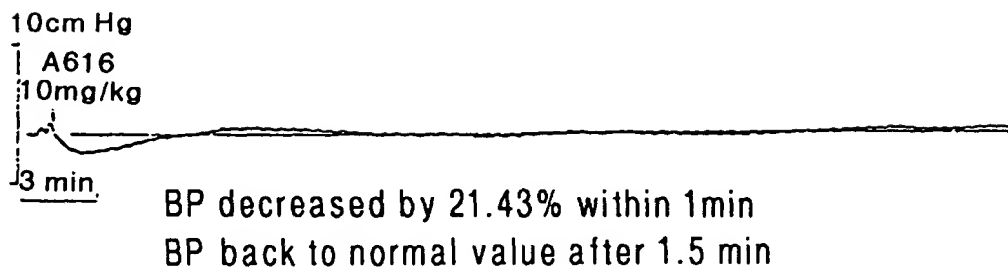
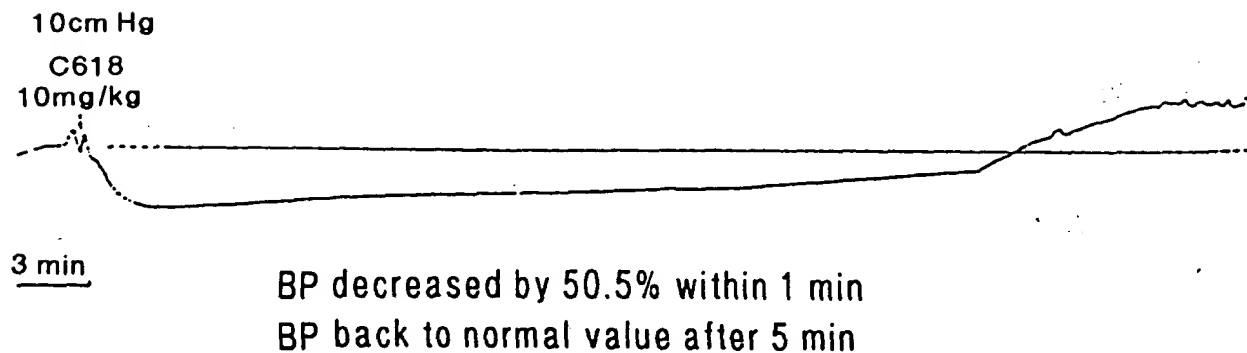


FIG.8B

EFFECT OF COCOA PROCYANIDIN FRACTION C ON
BLOOD PRESSURE



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EFFECT OF COCOA PROCYANIDIN FRACTIONS ON ARTERIAL BLOOD PRESSURE IN ANESTHESIZED GUINEA PIGS

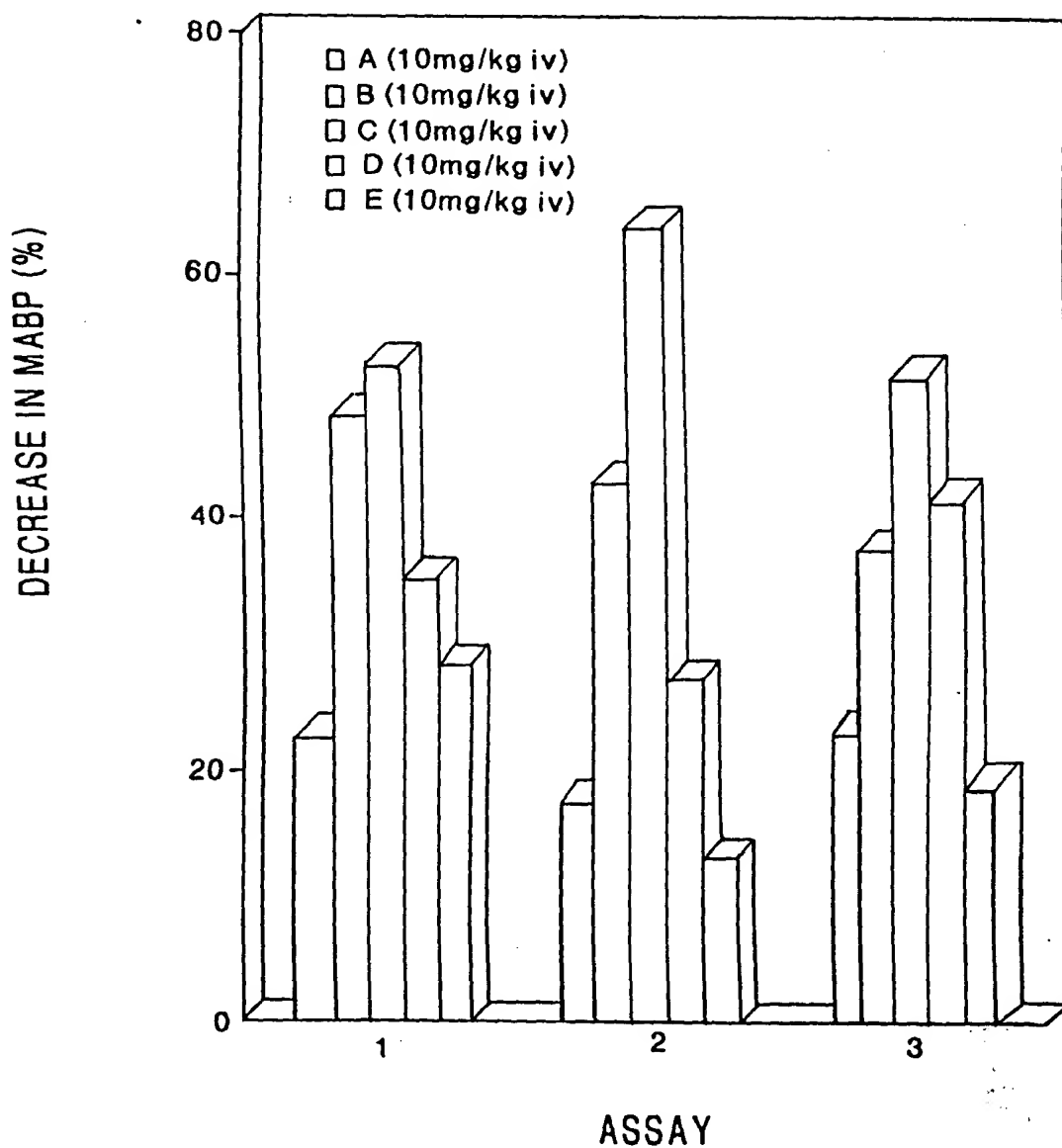


FIG.9

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EFFECT OF L-NMMA ON THE ALTERATIONS OF ARTERIAL
BLOOD PRESSURE IN ANESTHESIZED GUINEA PIGS INDUCED BY
COCOA PROCYANIDIN FRACTION C

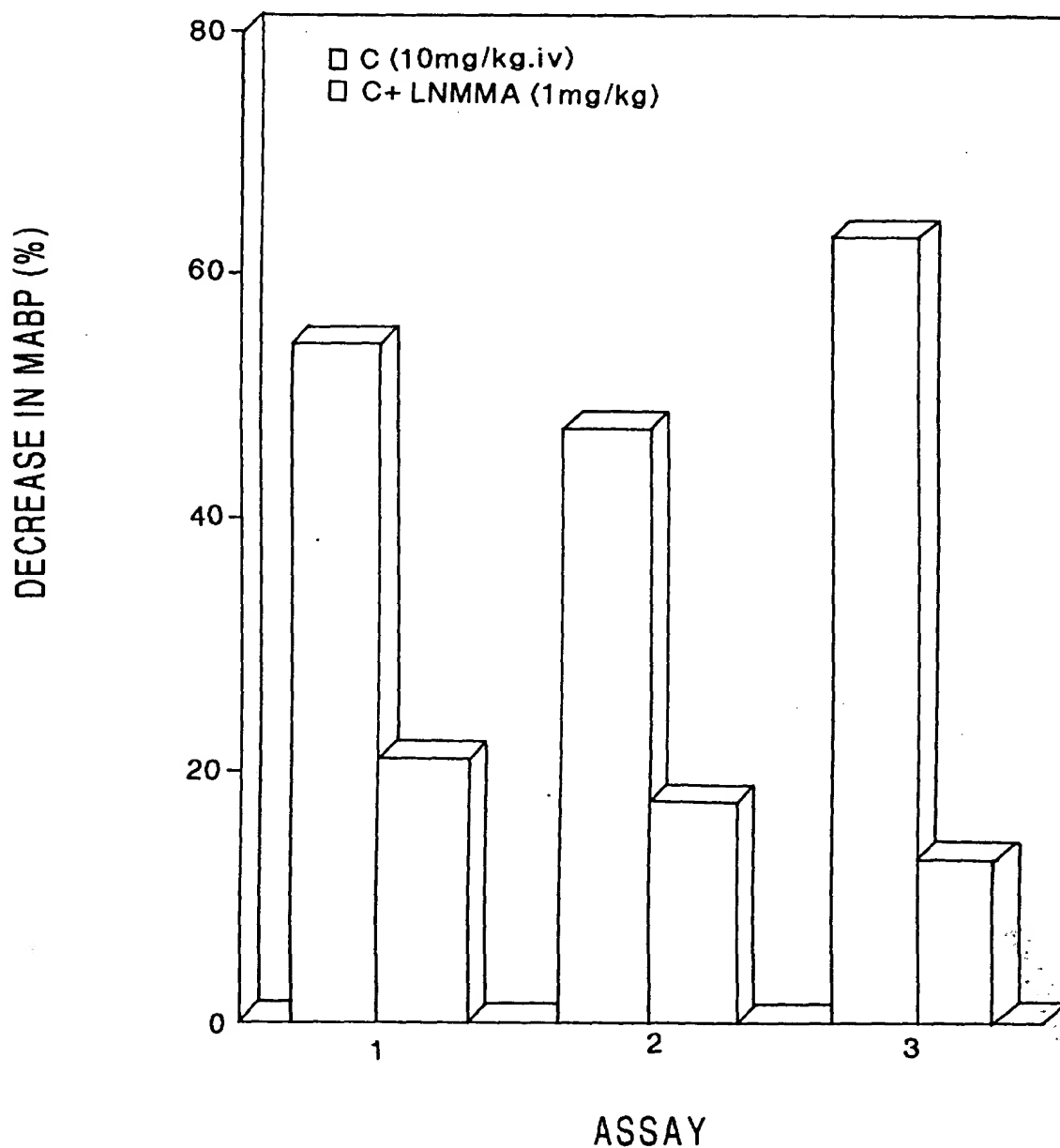


FIG.10



EFFECT OF BRADYKININ ON NO PRODUCTION BY HUVEC

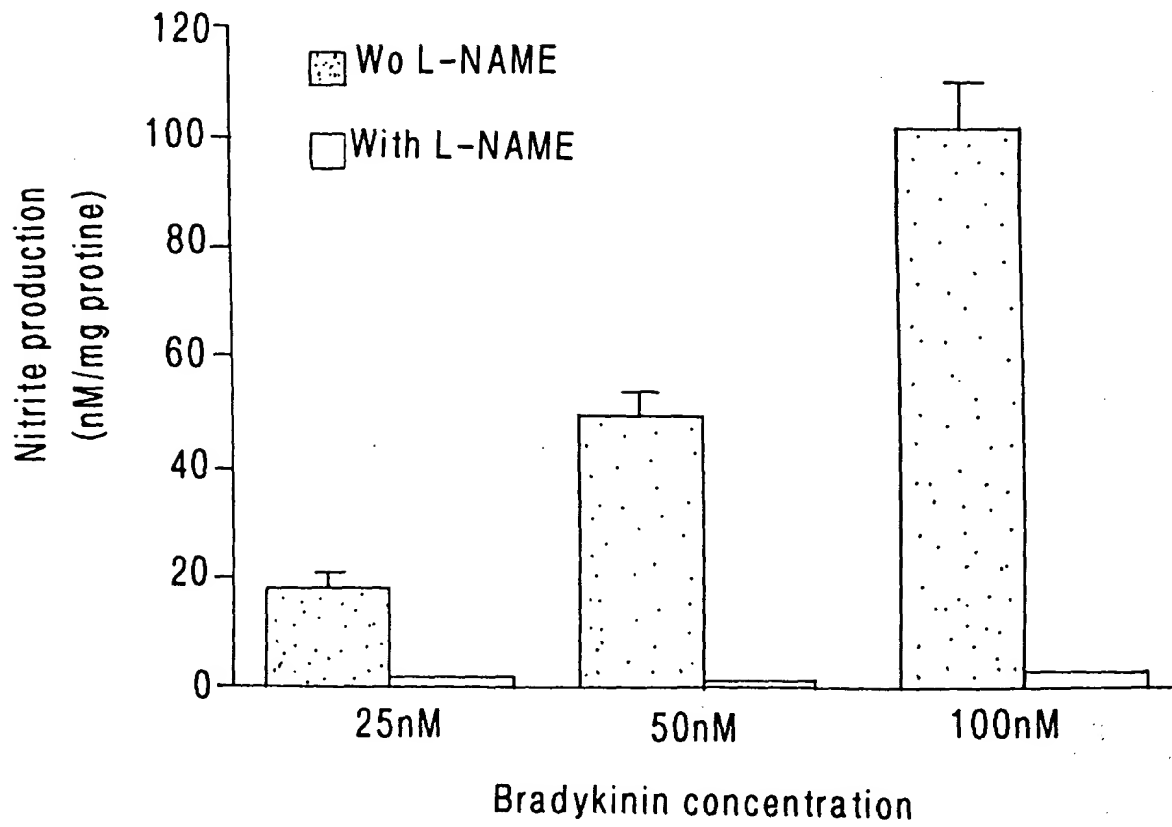


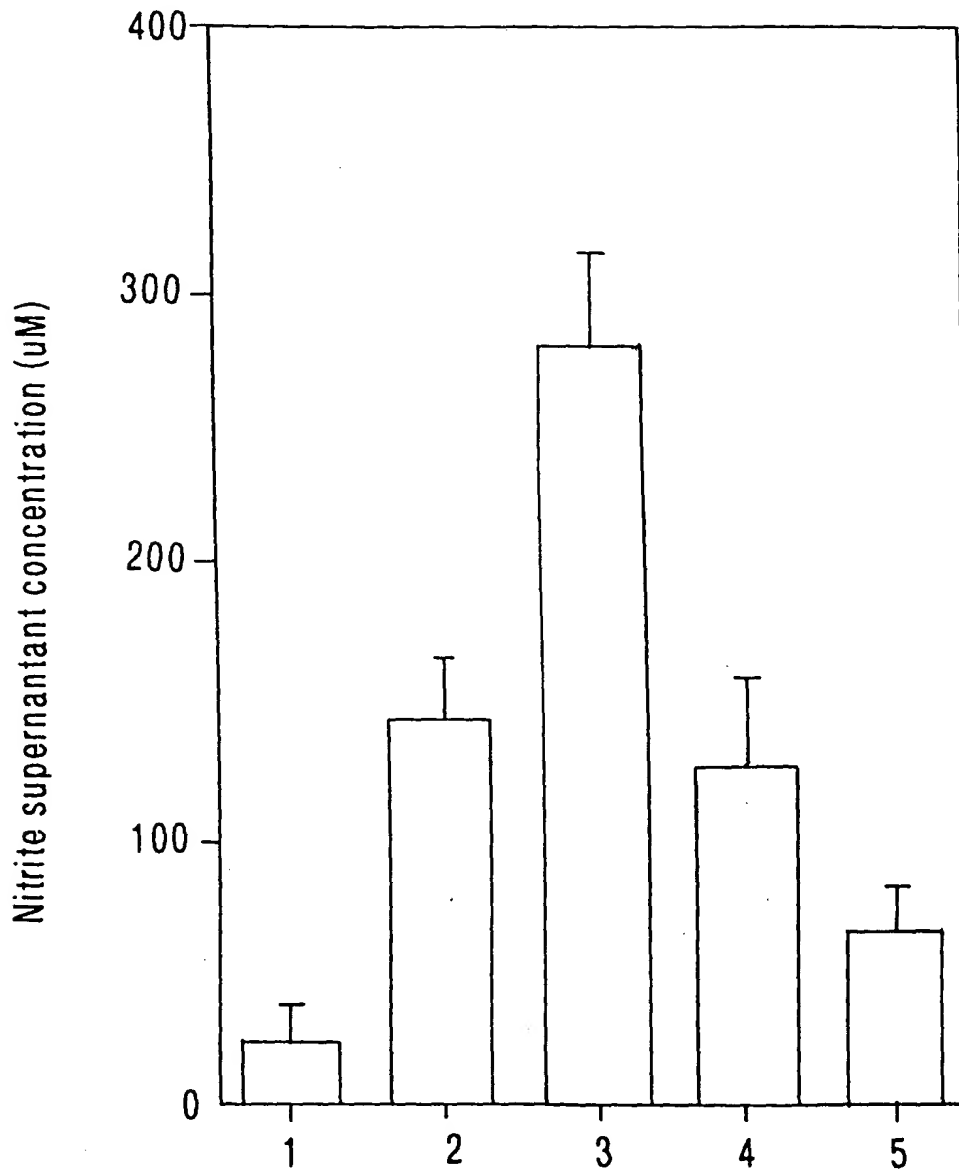
FIG.11

APPROVED	O.S. FIG.	
KEY	CLASS	SUBCLASS
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EFFECT OF COCOA PROCYANIDIN FRACTIONS ON NO PRODUCTION BY HUVEC



Samples A,B,D and E
(mean of 3 assays)

FIG.12

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Figure A: Effect of Cocoa Procyanidin Fractions on Macrophage

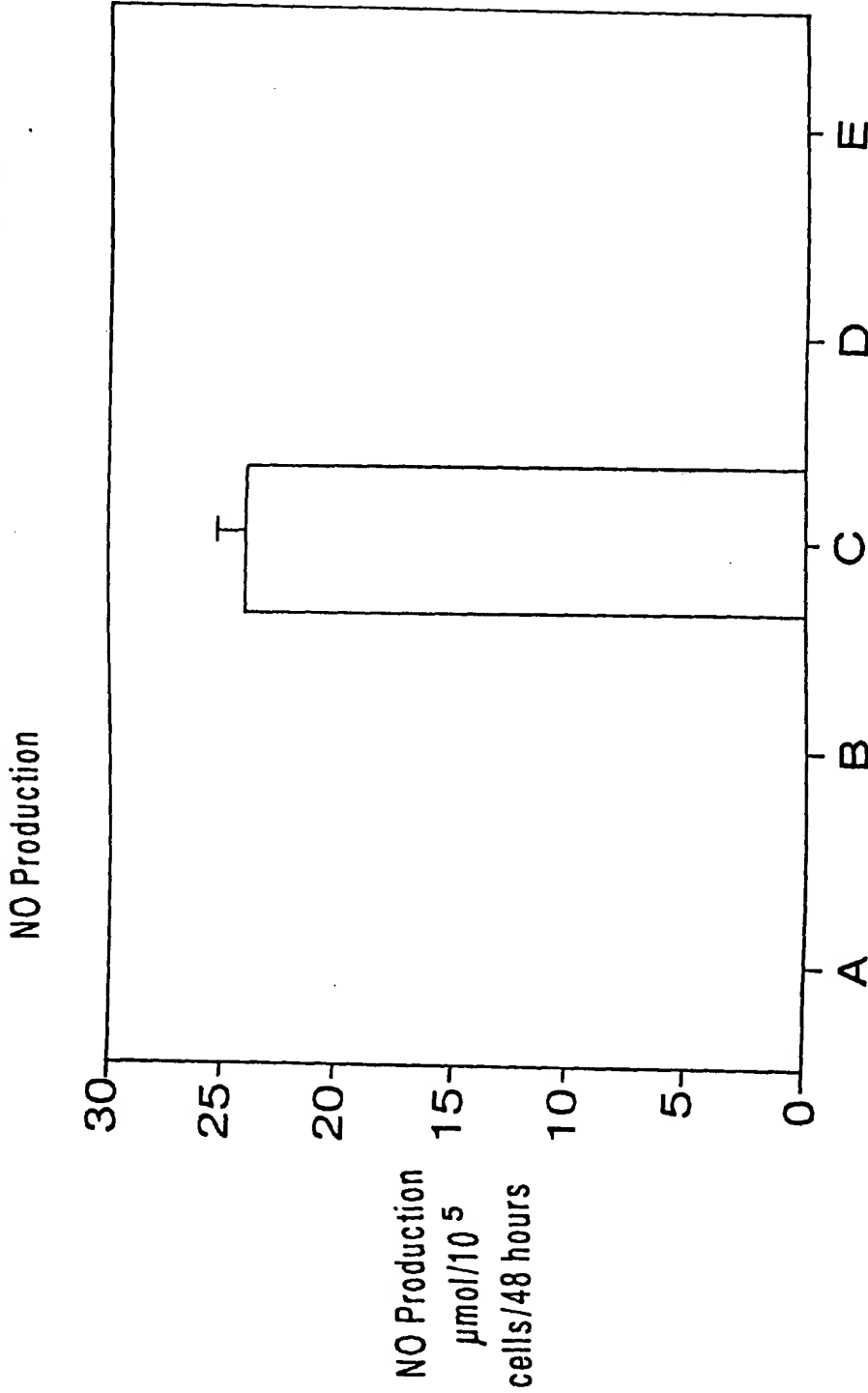
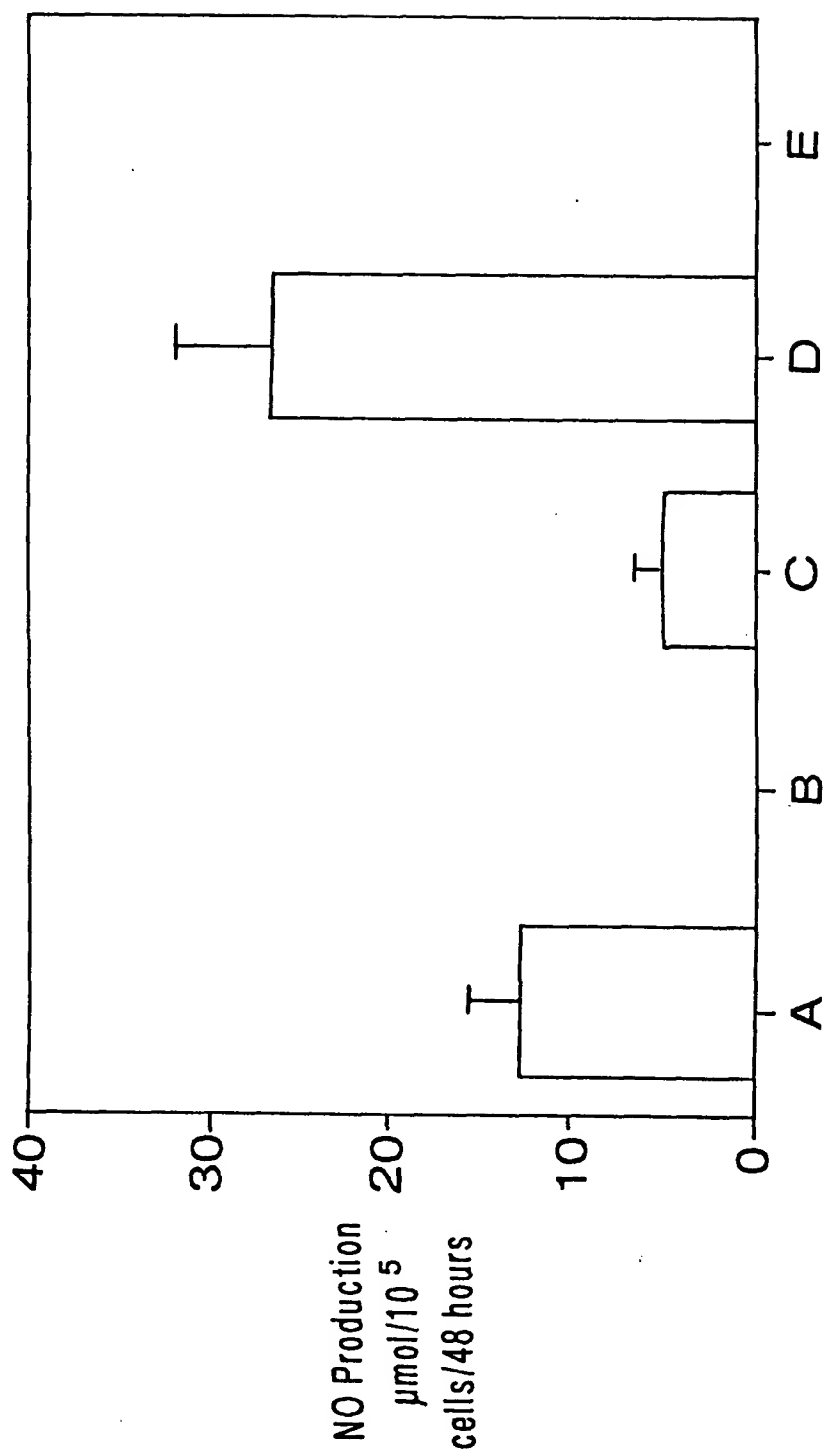


FIG.13

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Figure B: Effect of Cocoa Procyanidin Fractions on LPS Induced and γ -Interferon Primed Macrophages



Cocoa Procyanidin Fractions

FIG.14

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FIG.15A

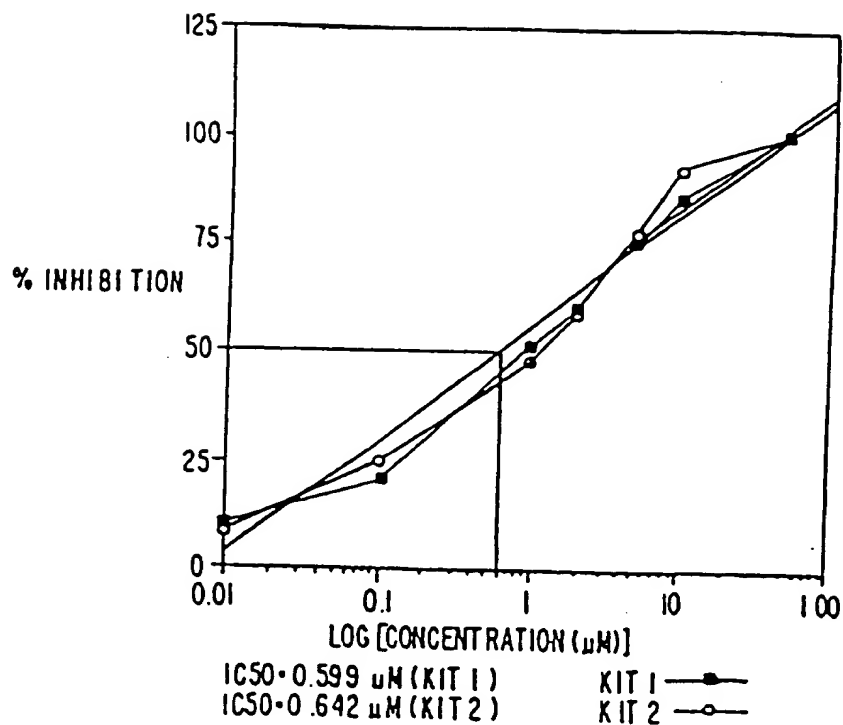
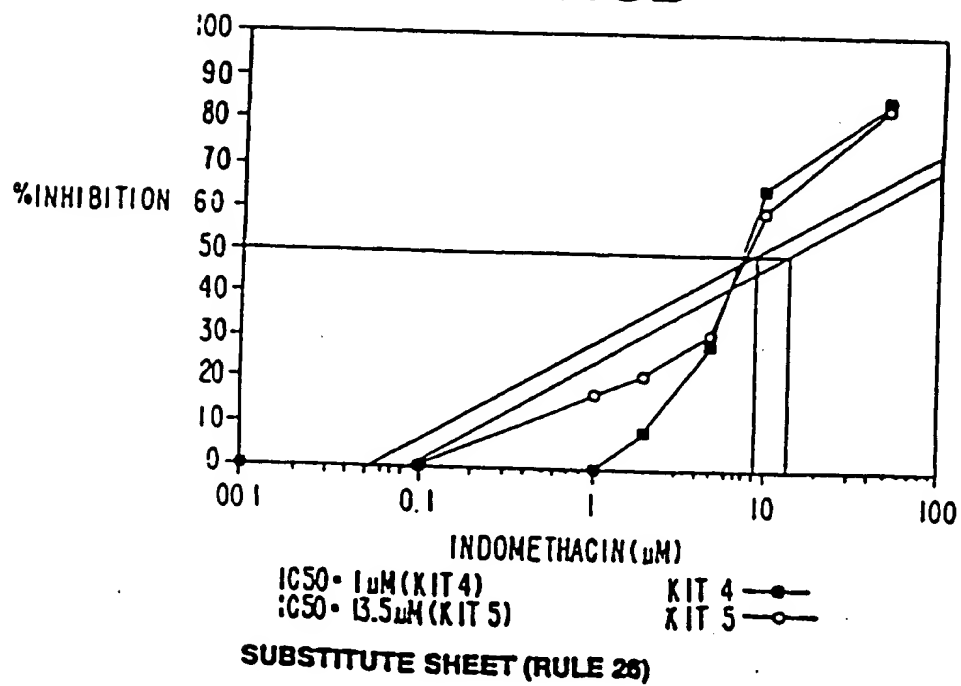


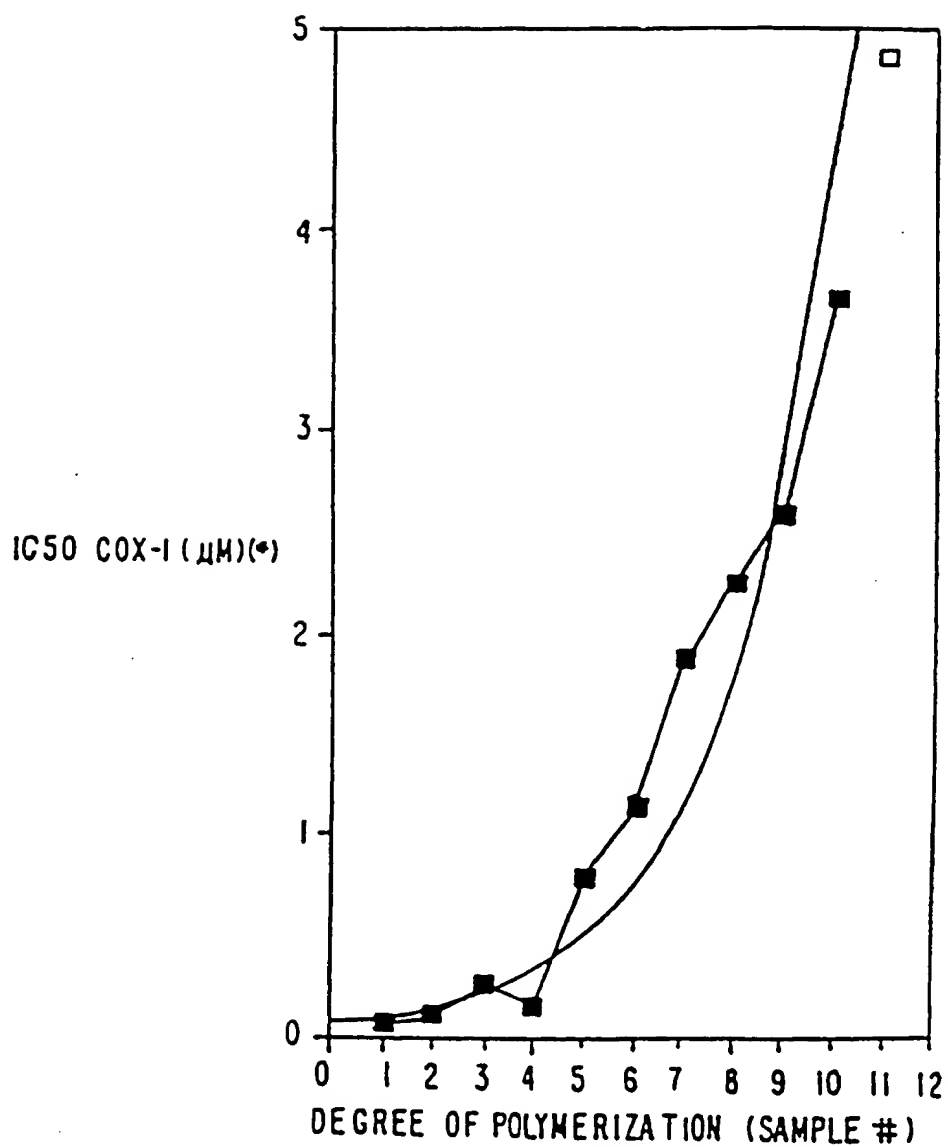
FIG.15B



APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
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FIG.16A

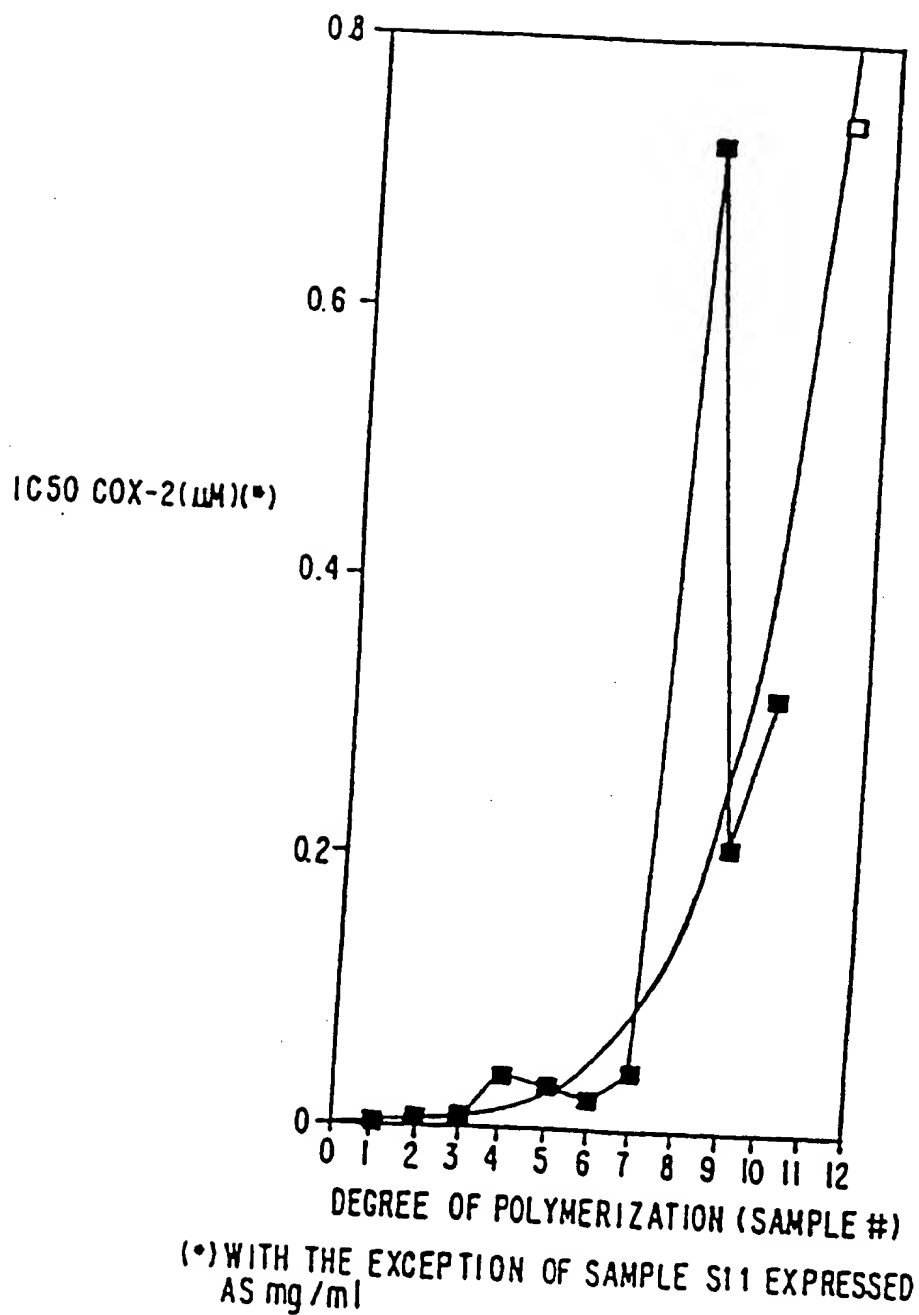


(*) WITH THE EXCEPTION OF SAMPLE SII EXPRESSED AS mg/ml

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
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FIG.16B



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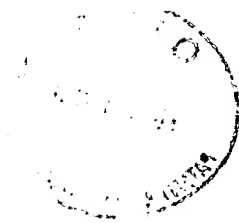
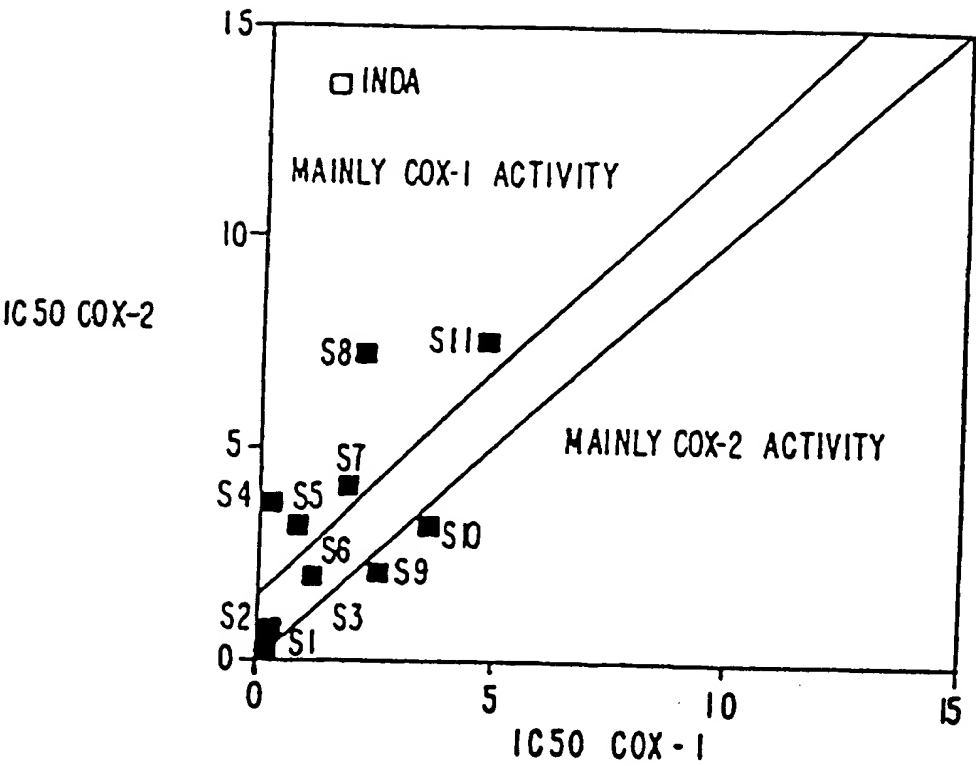


FIG.17



(*) WITH THE EXEPTION OF SAMPLE S11

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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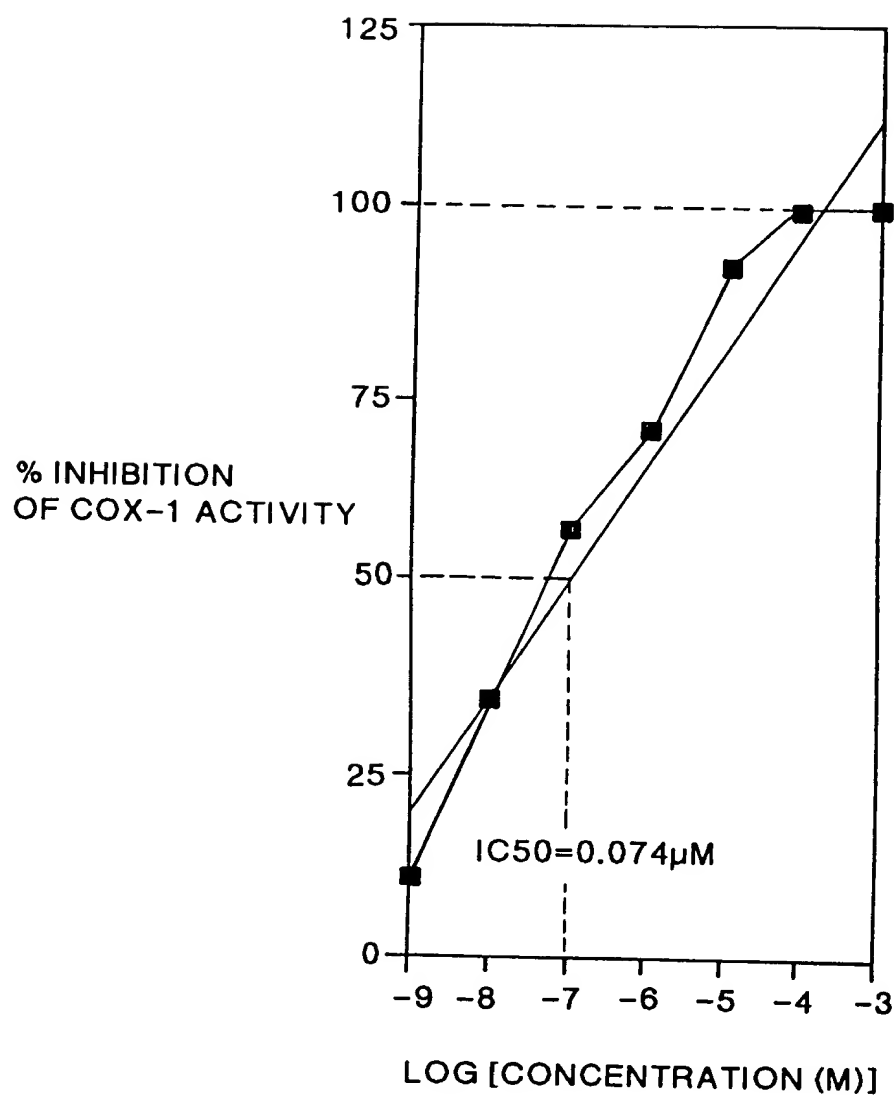


FIG.18A

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
CRAFTSMAN		

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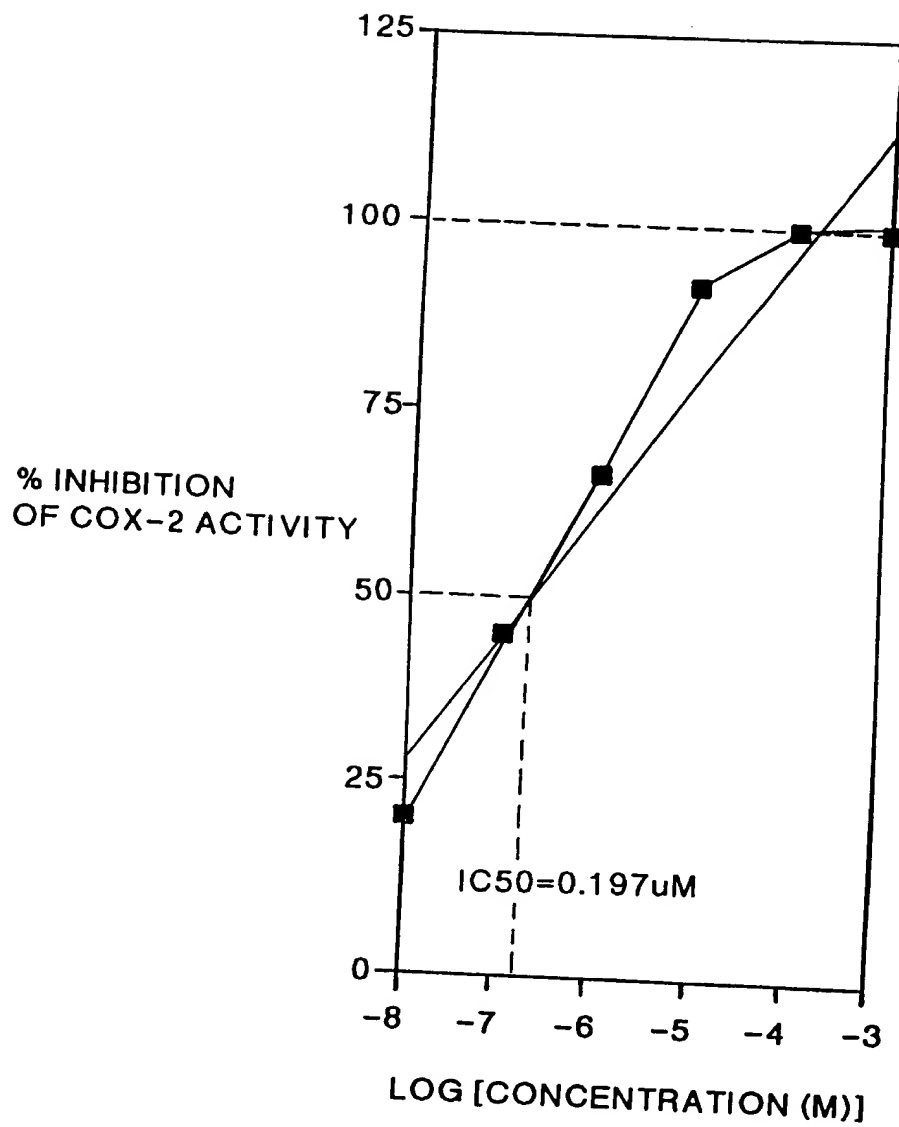


FIG.18B

APPROVED	D.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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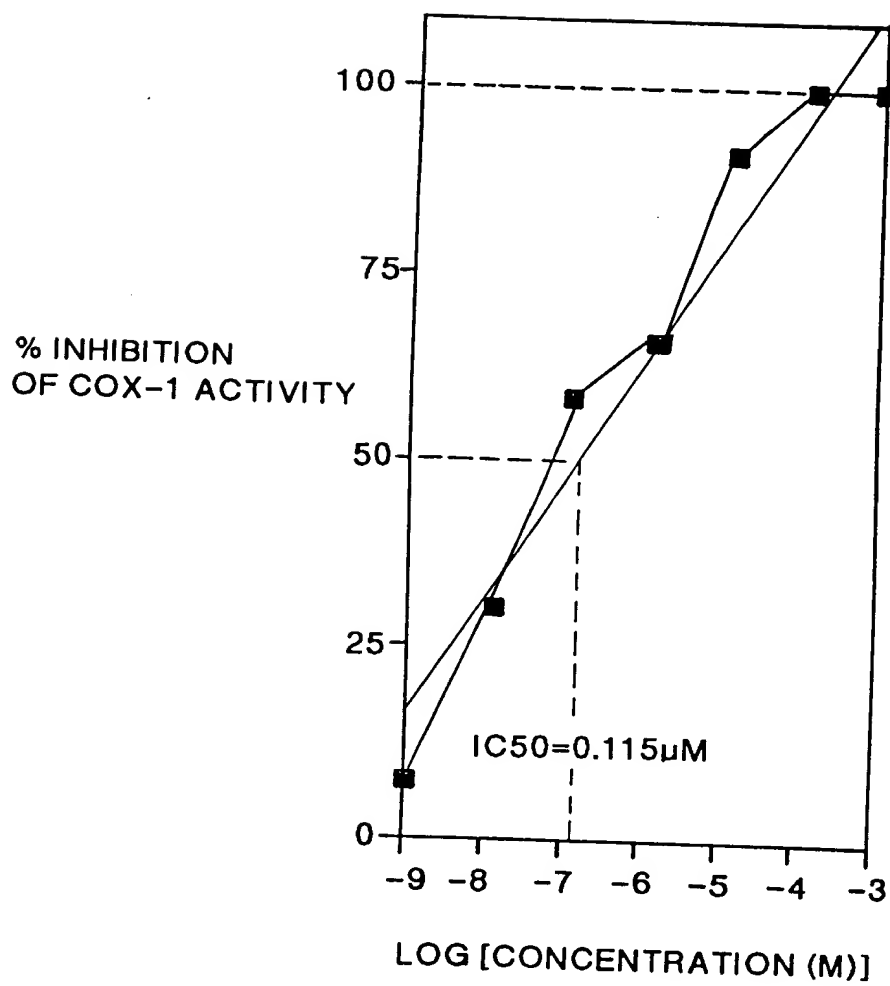


FIG.18C

APPROVED	J.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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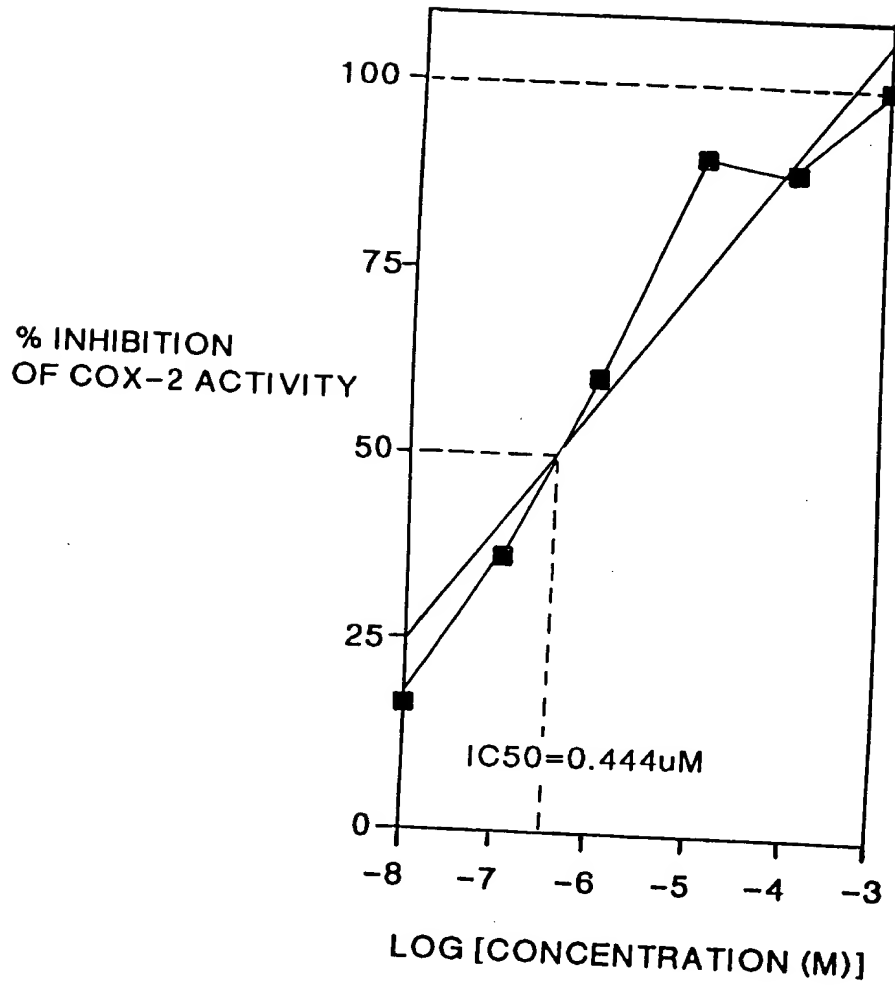


FIG.18D

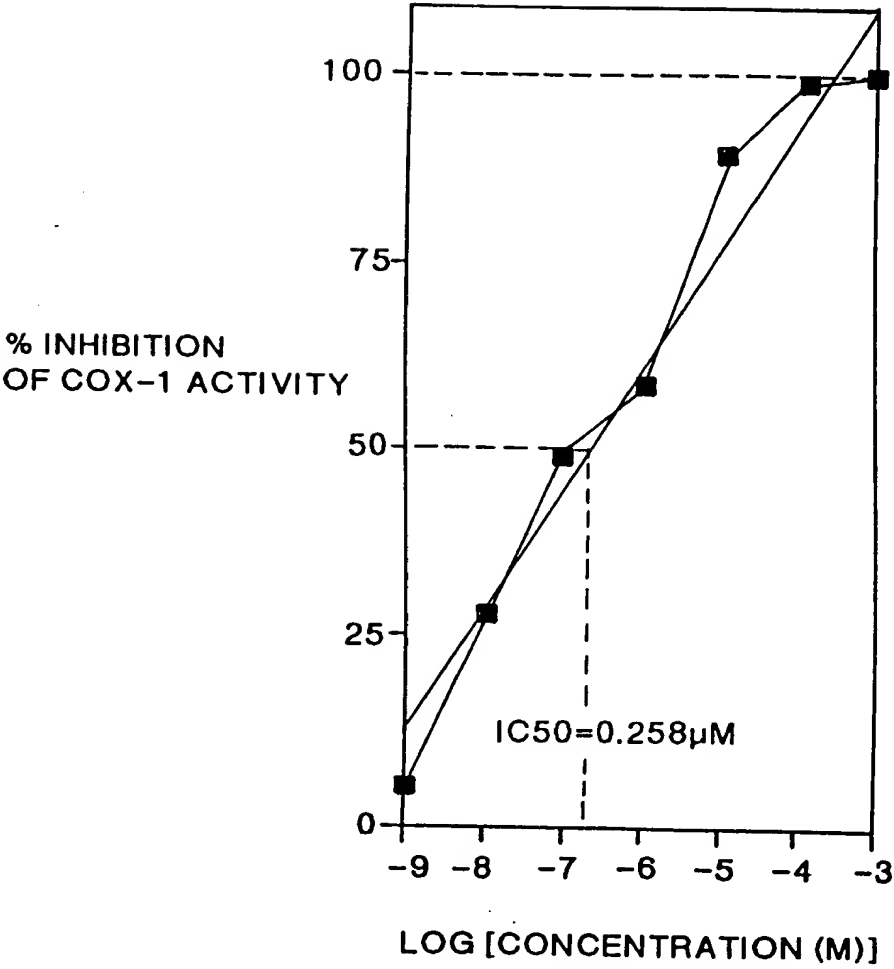


FIG.18E

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
RAFTSMAN		

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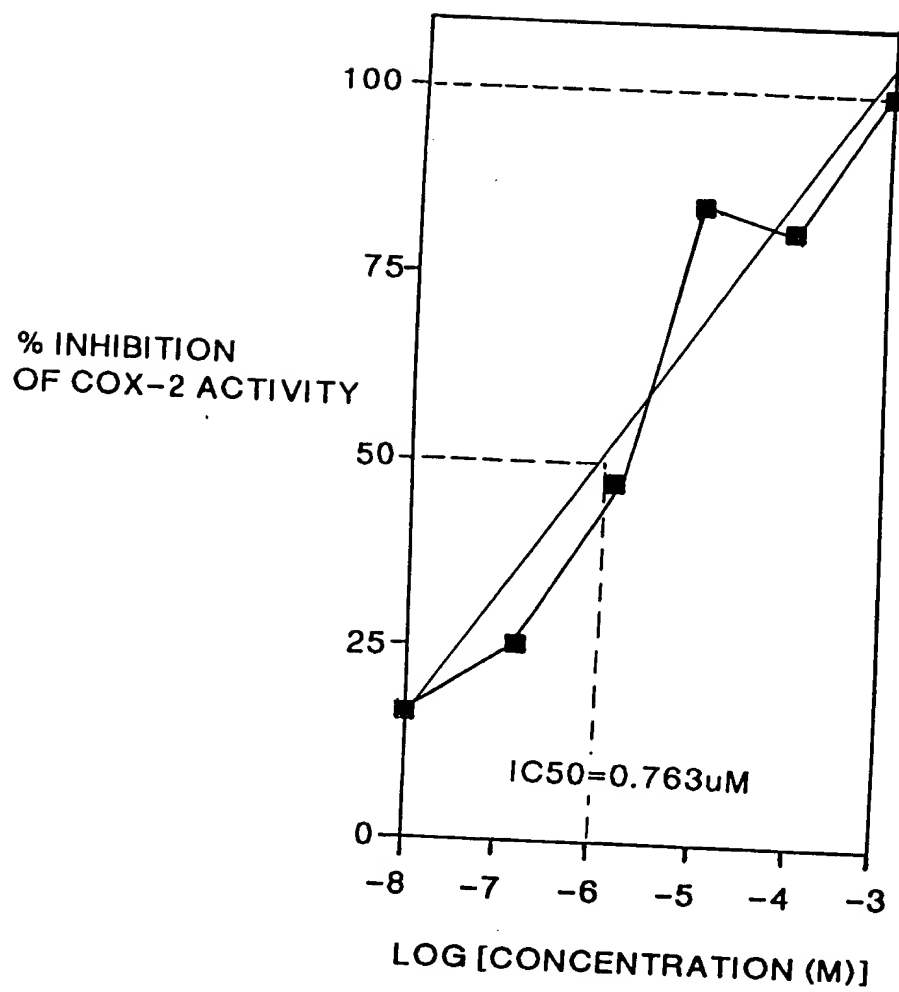


FIG.18F

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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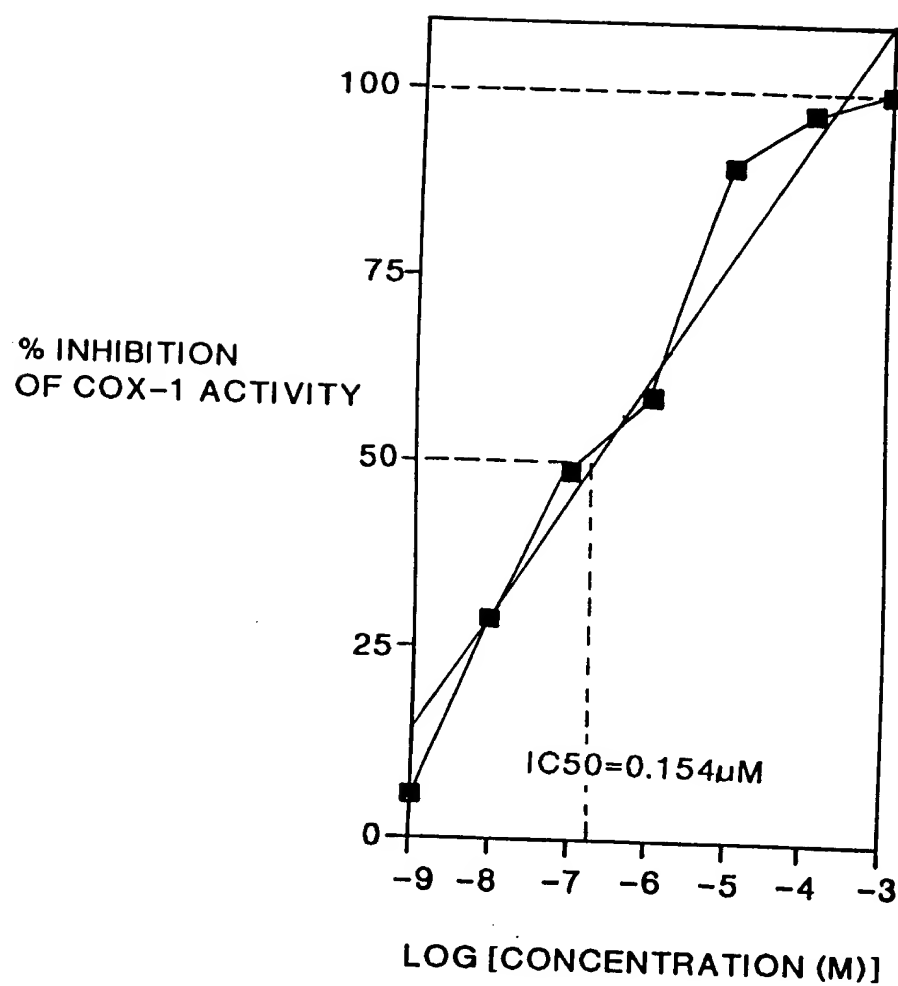


FIG.18G

APPROVED	O.C. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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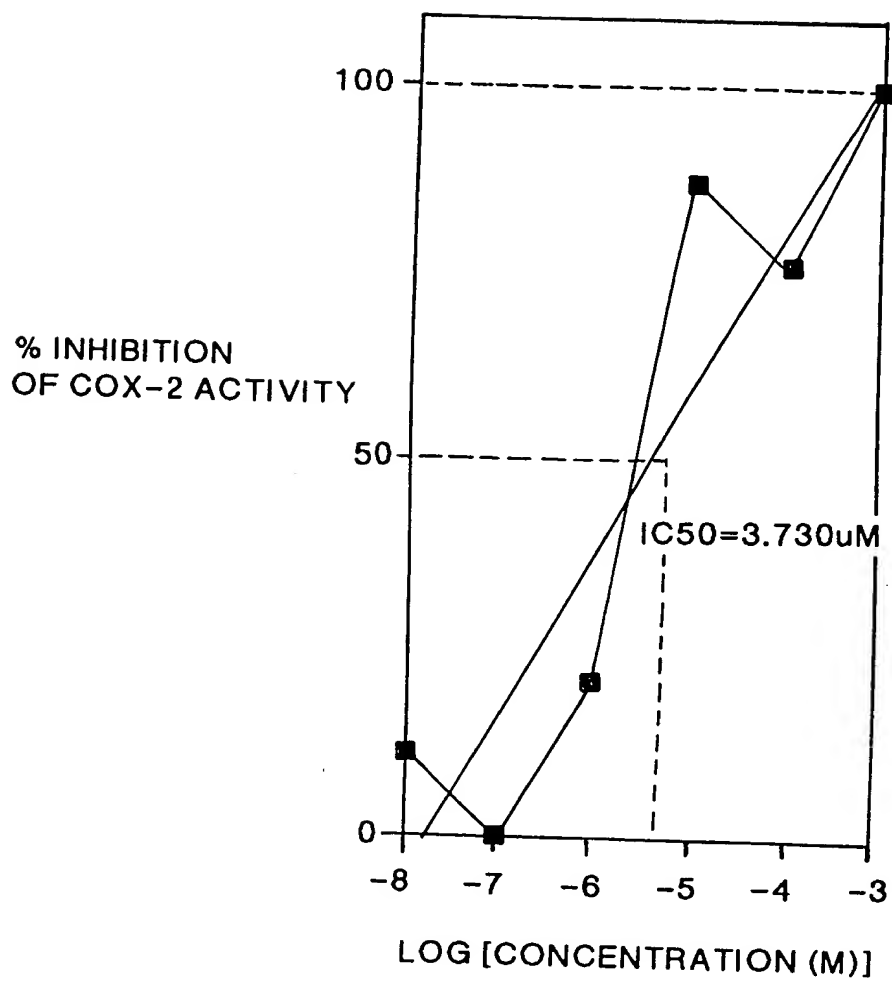


FIG.18H

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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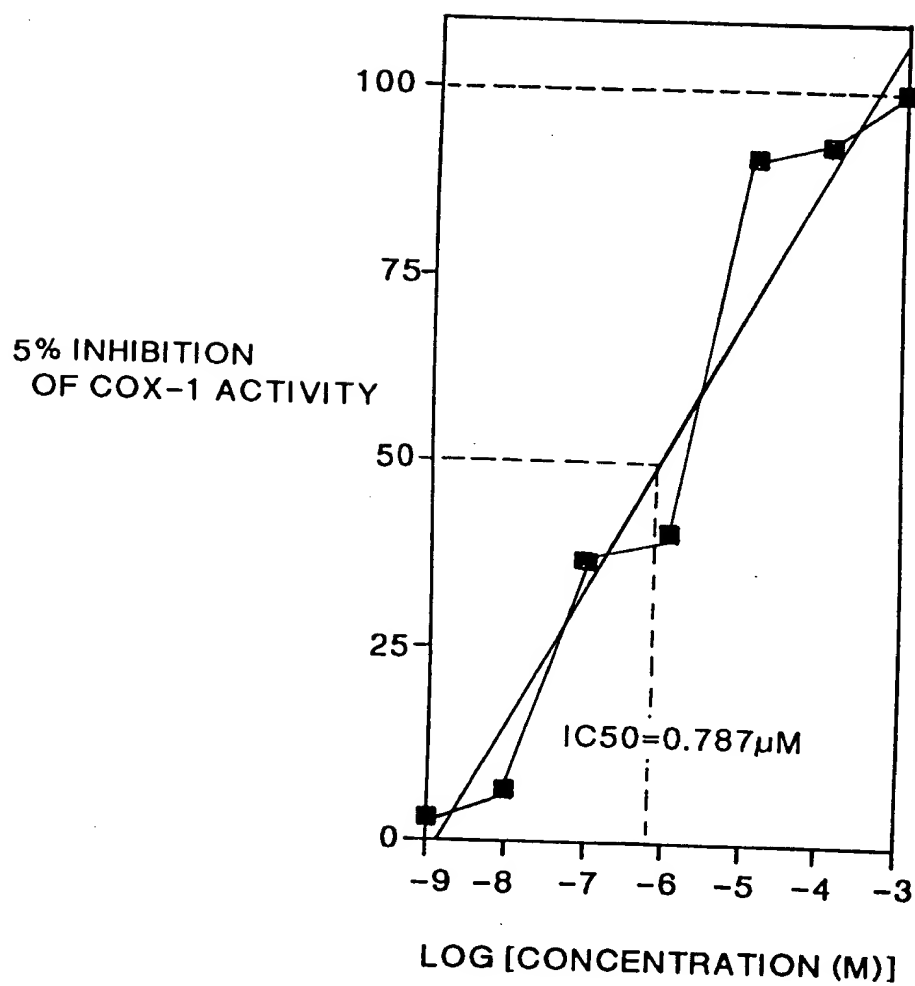


FIG.18 I

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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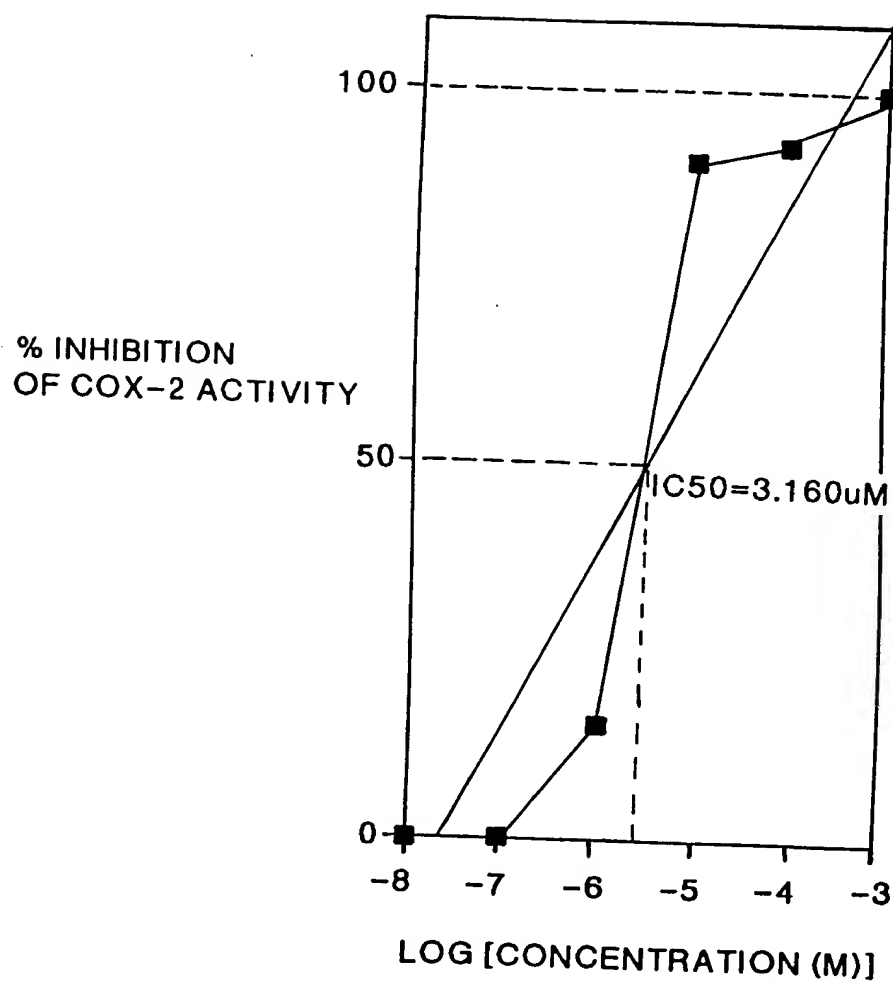


FIG.18J

APPROVED	D.C. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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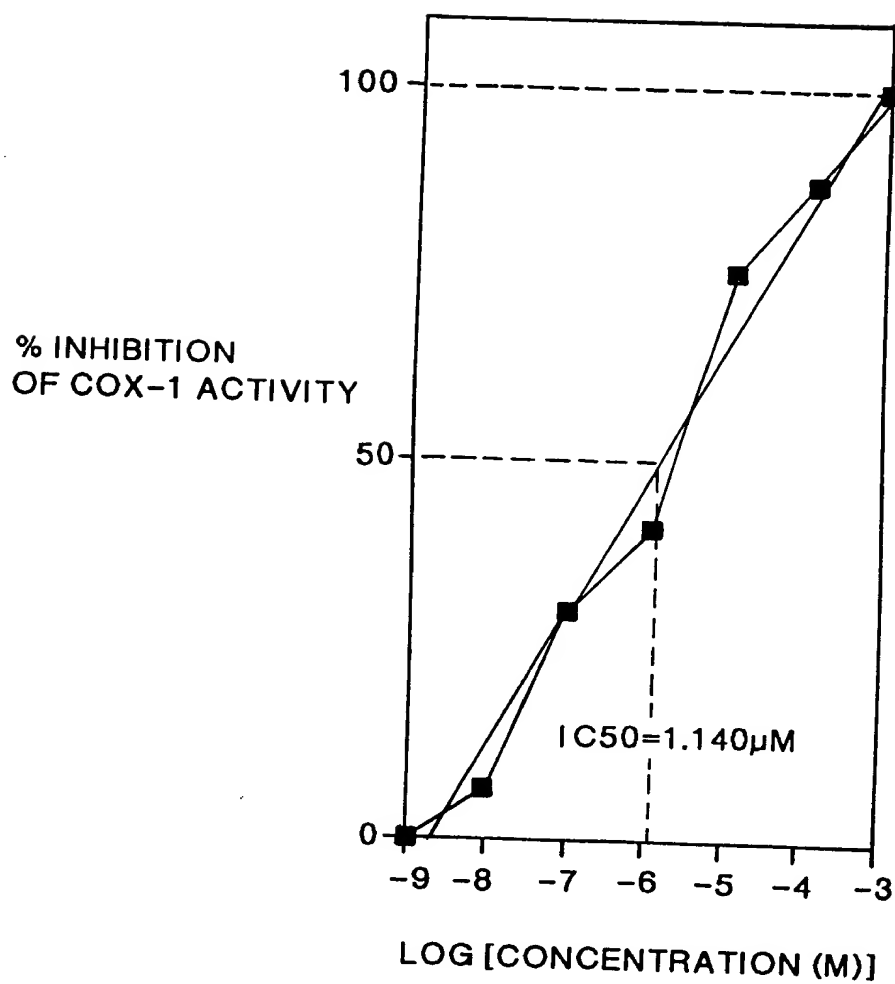


FIG.18K

APPROVED	C.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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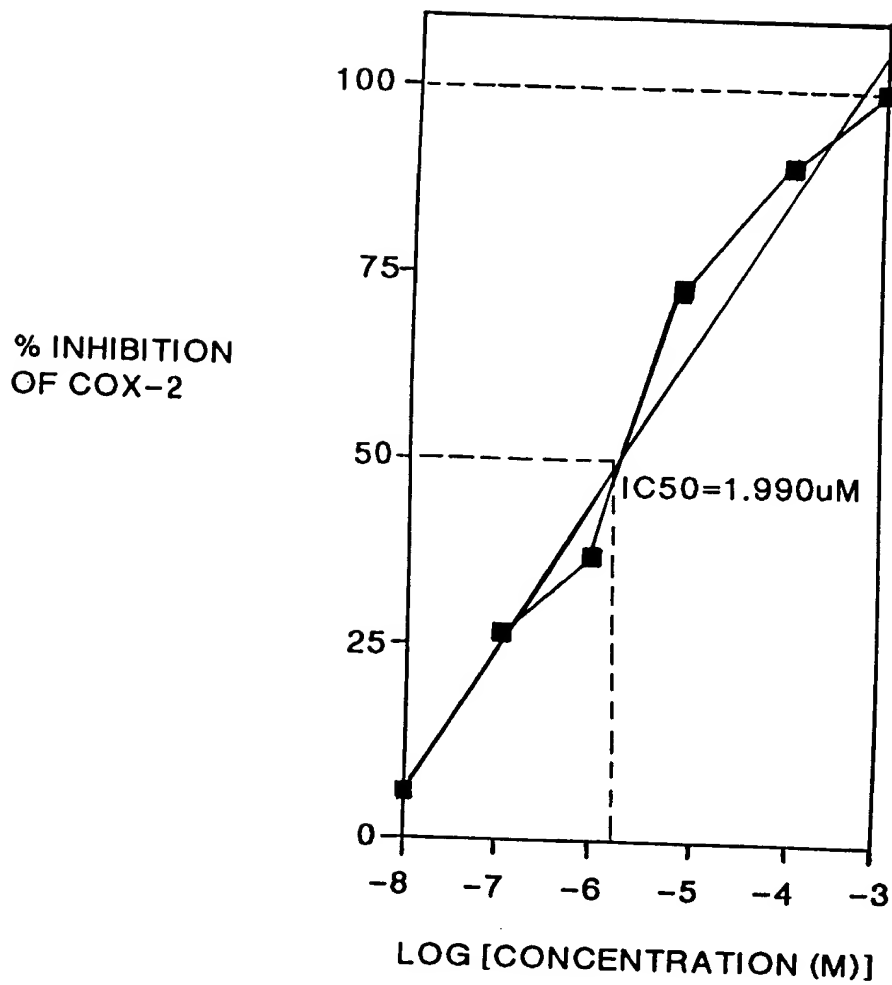
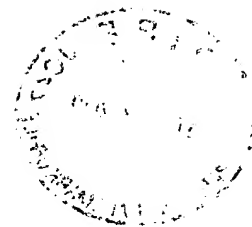


FIG.18L

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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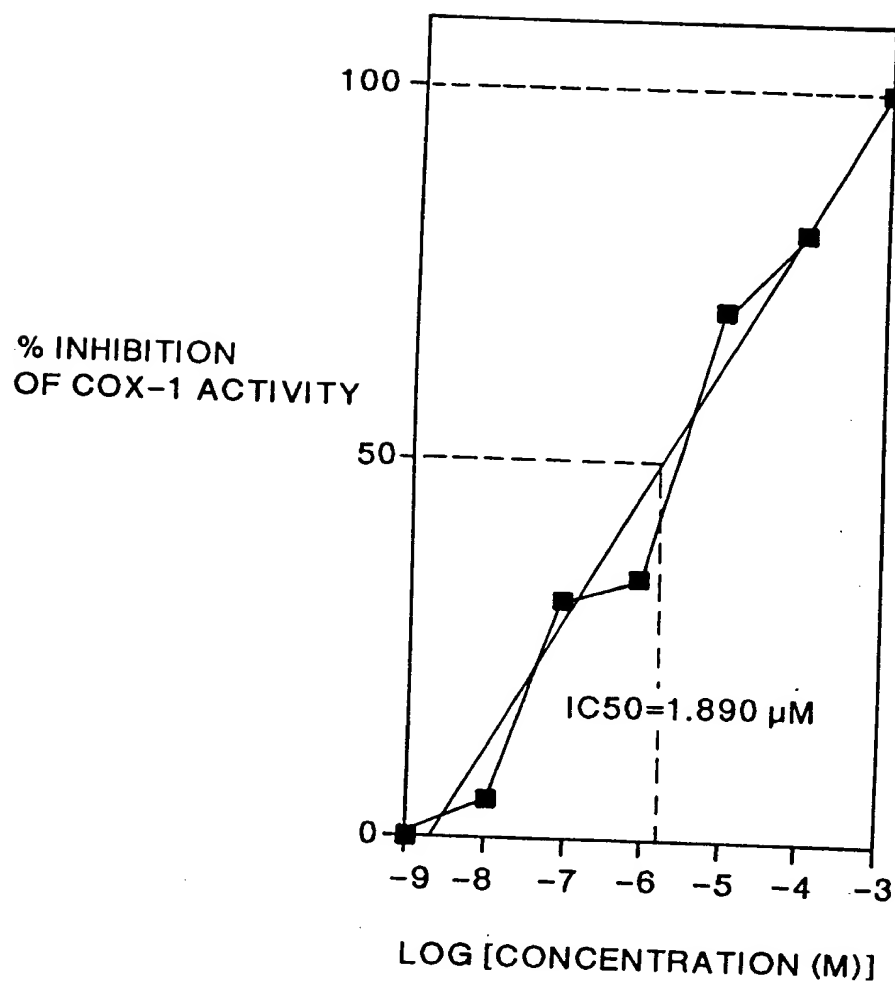


FIG.18M

APPROVED	O.S. FIG.	
*BY	*CLASS	SUBCLASS
DRAFTSMAN		

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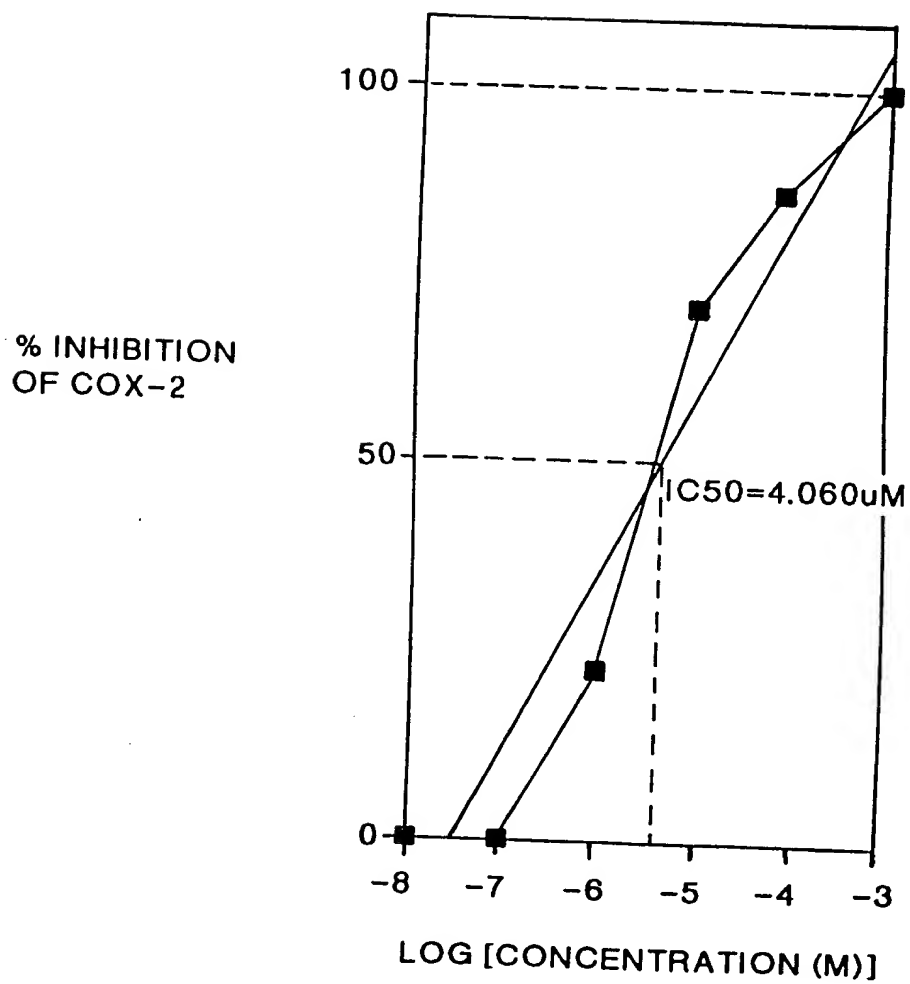


FIG.18N

APPROVED	3.6. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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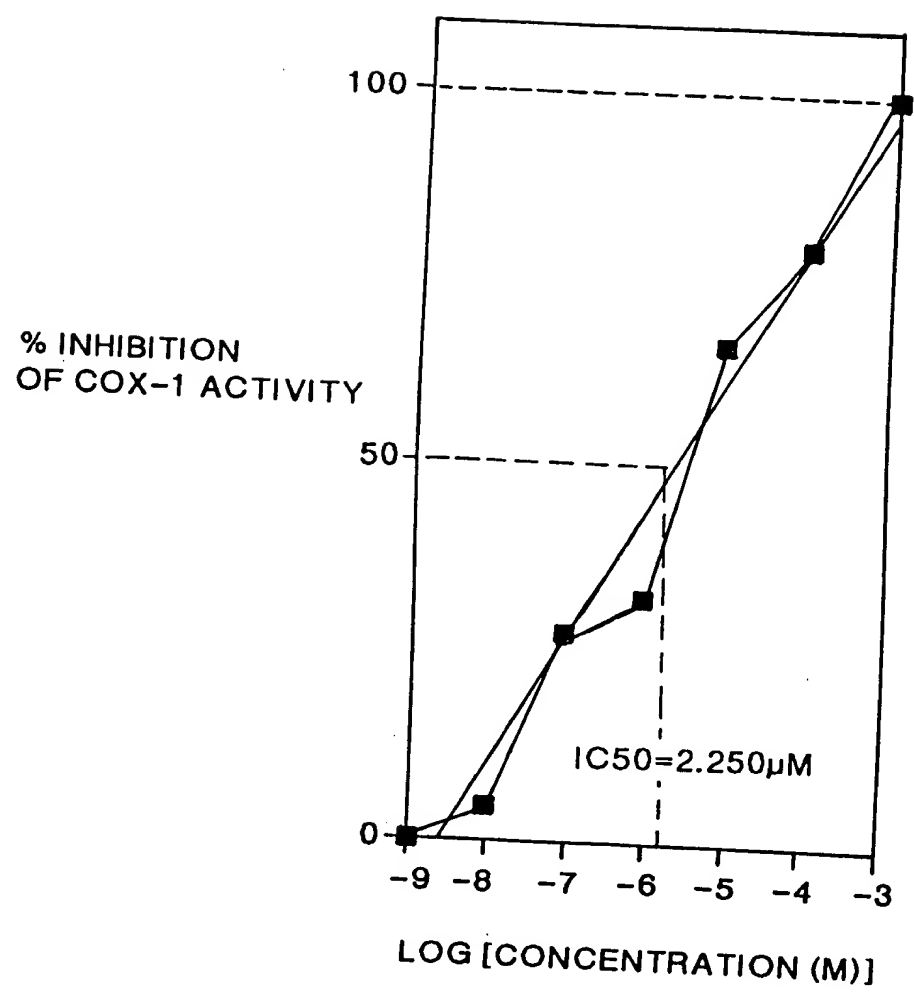


FIG.180

% INHIBITION
OF COX-2

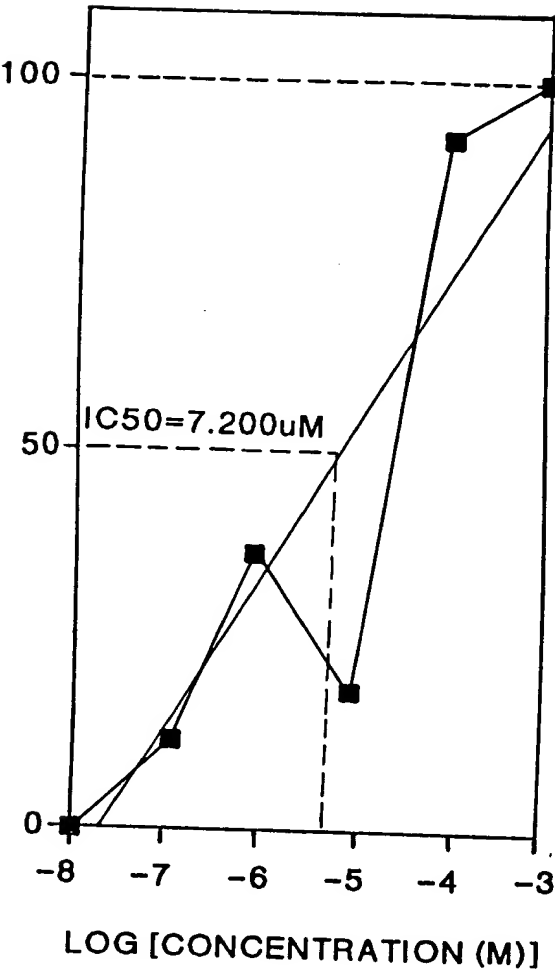


FIG.18P

APPROVED	J.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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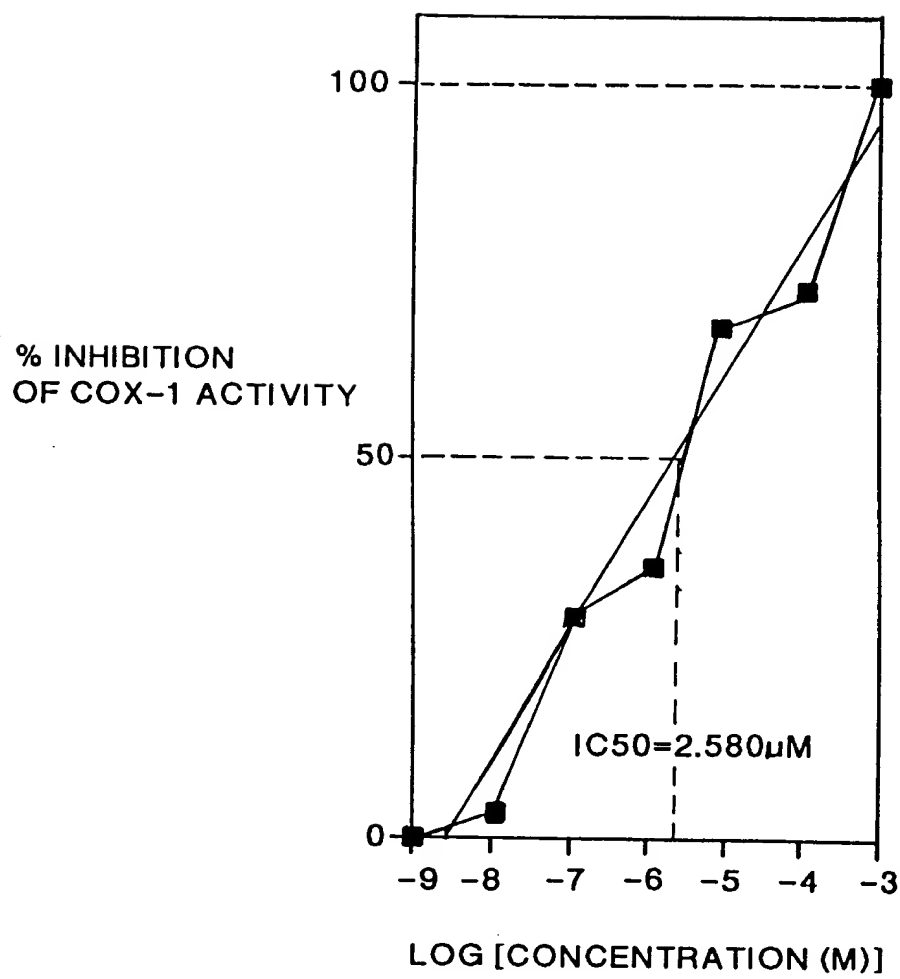


FIG.18Q

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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% INHIBITION
OF COX-2

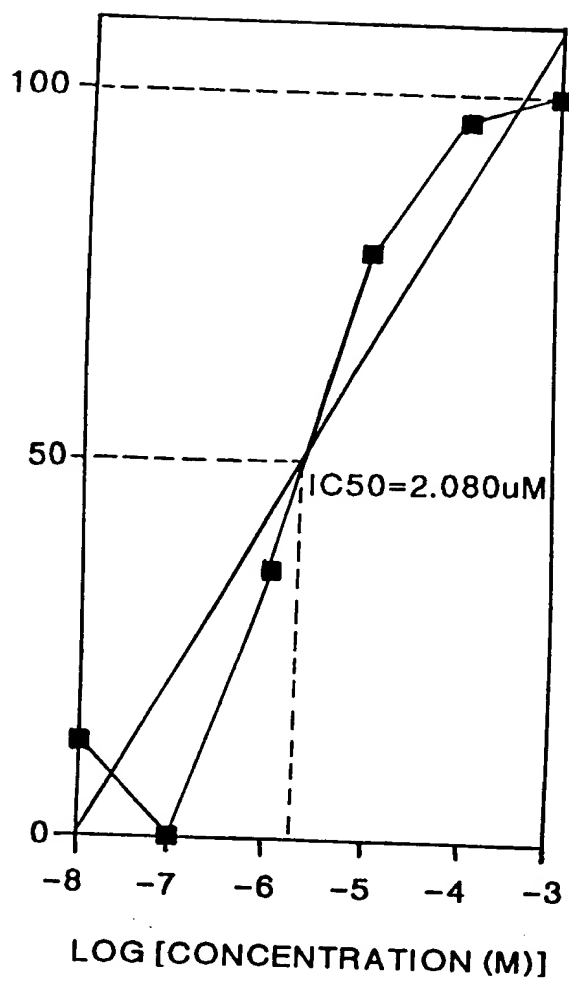


FIG.18R

APPROVED	C.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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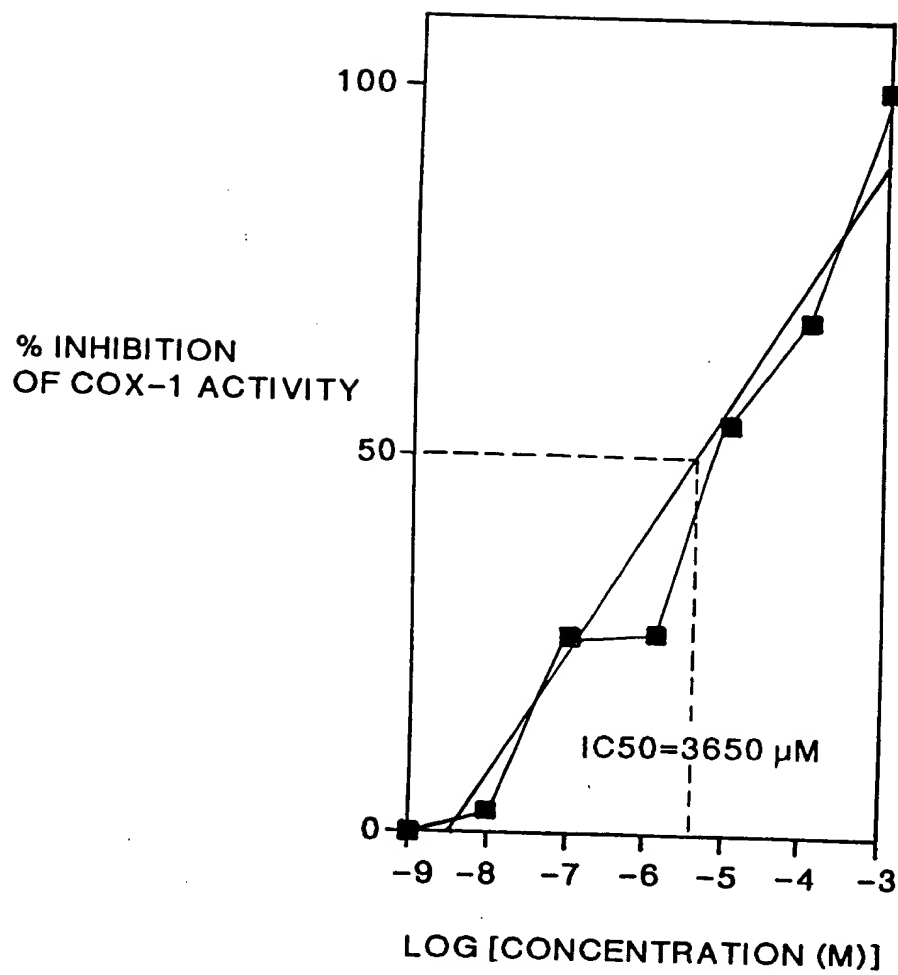


FIG.18S

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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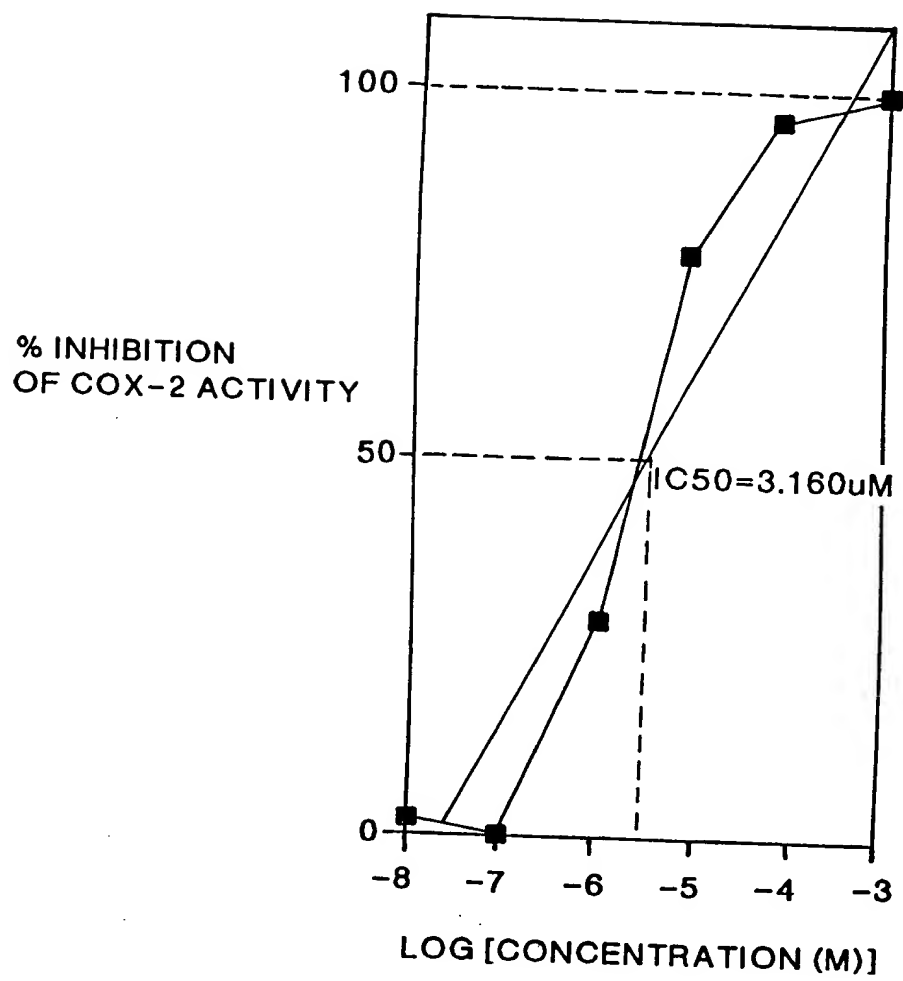


FIG.18T



% INHIBITION
OF COX- 1 ACTIVITY

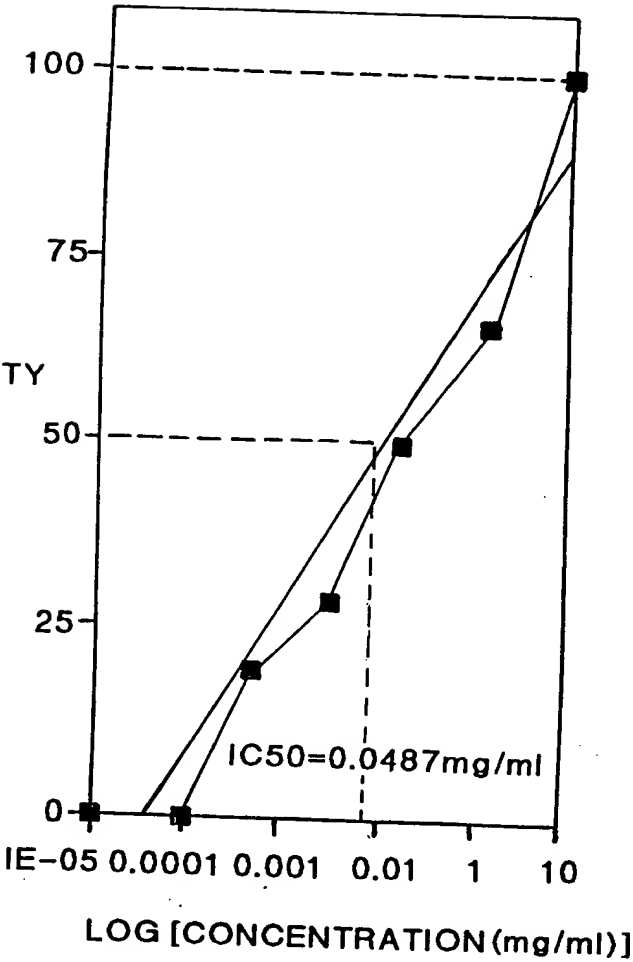


FIG.18U

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN		

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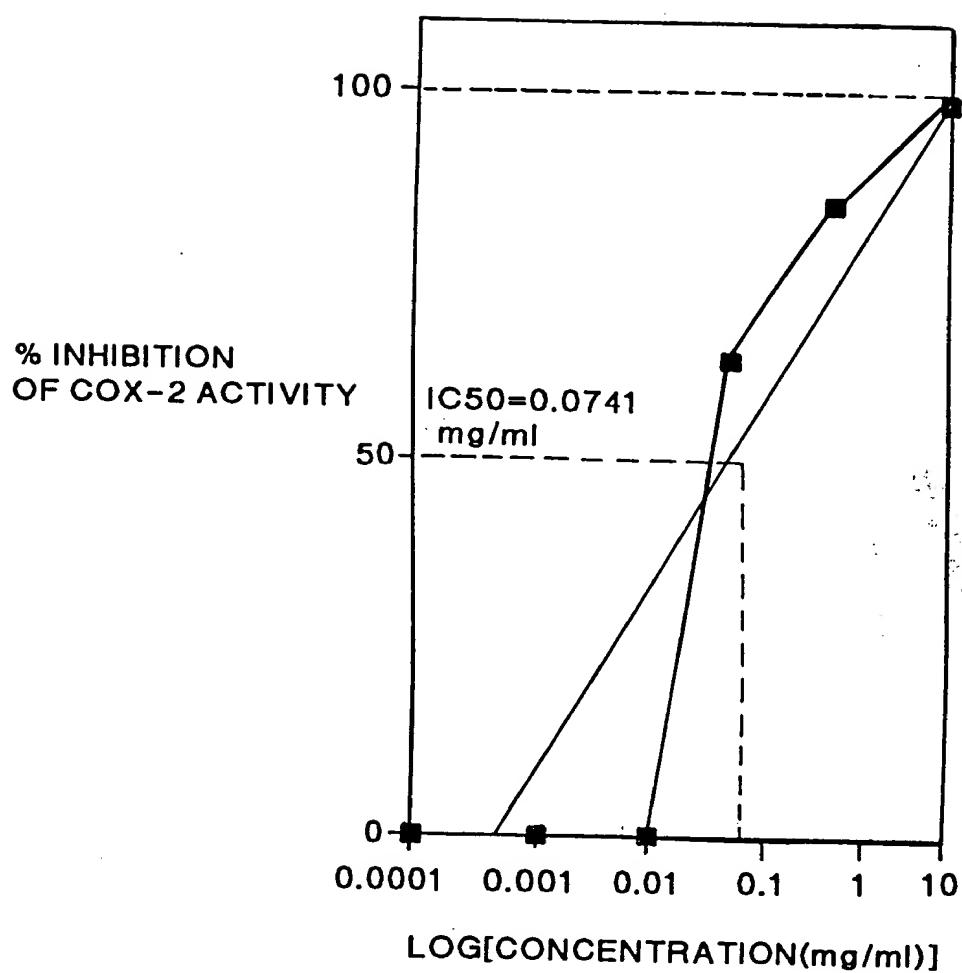
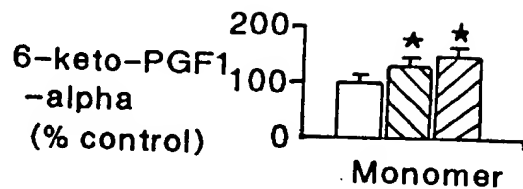
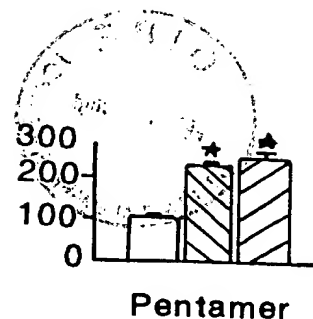


FIG.18V

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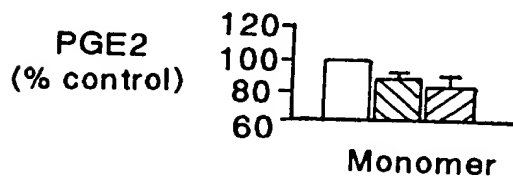


6-keto-PGF1
-alpha
(% control)

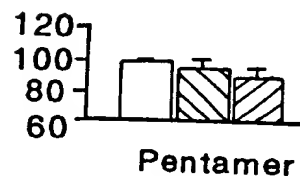


10uM 20uM 30uM

FIG.19A

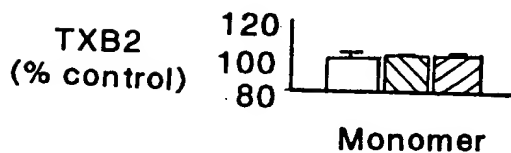


PGE2
(% control)

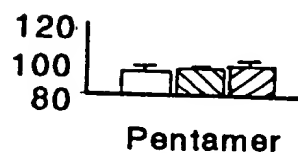


10uM 20uM 30uM

FIG.19B

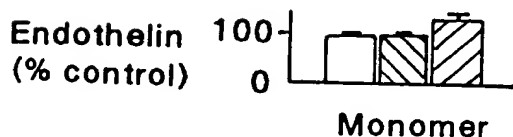


TXB2
(% control)

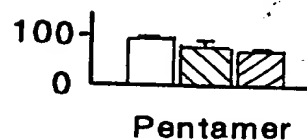


10uM 20uM 30uM

FIG.19C



Endothelin
(% control)



10uM 20uM 30uM

FIG.19D

APPROVED	G. G. FIG.	
BY	CLASS	SUBCLASS
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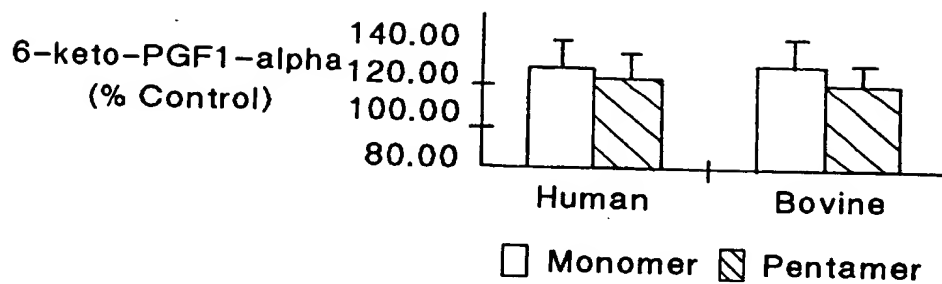


FIG.20A

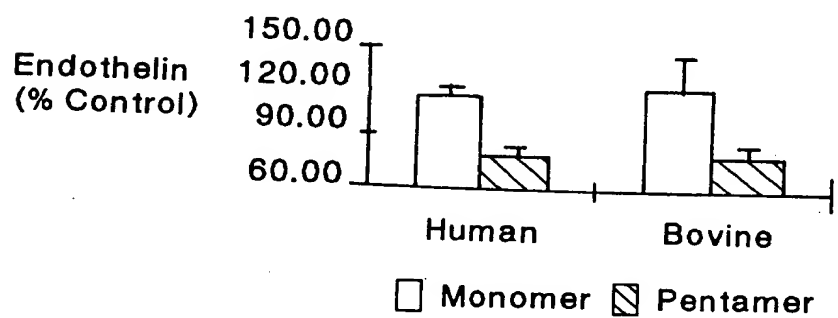
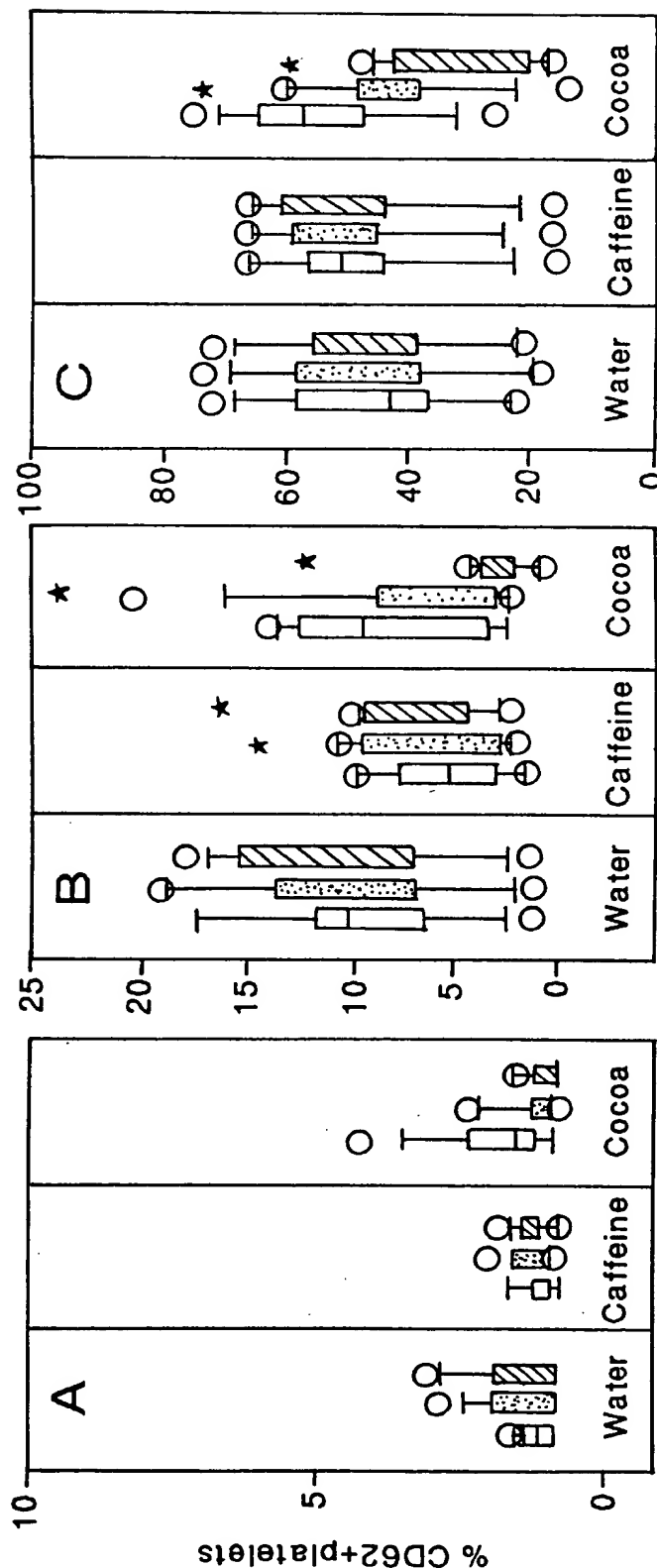


FIG.20B

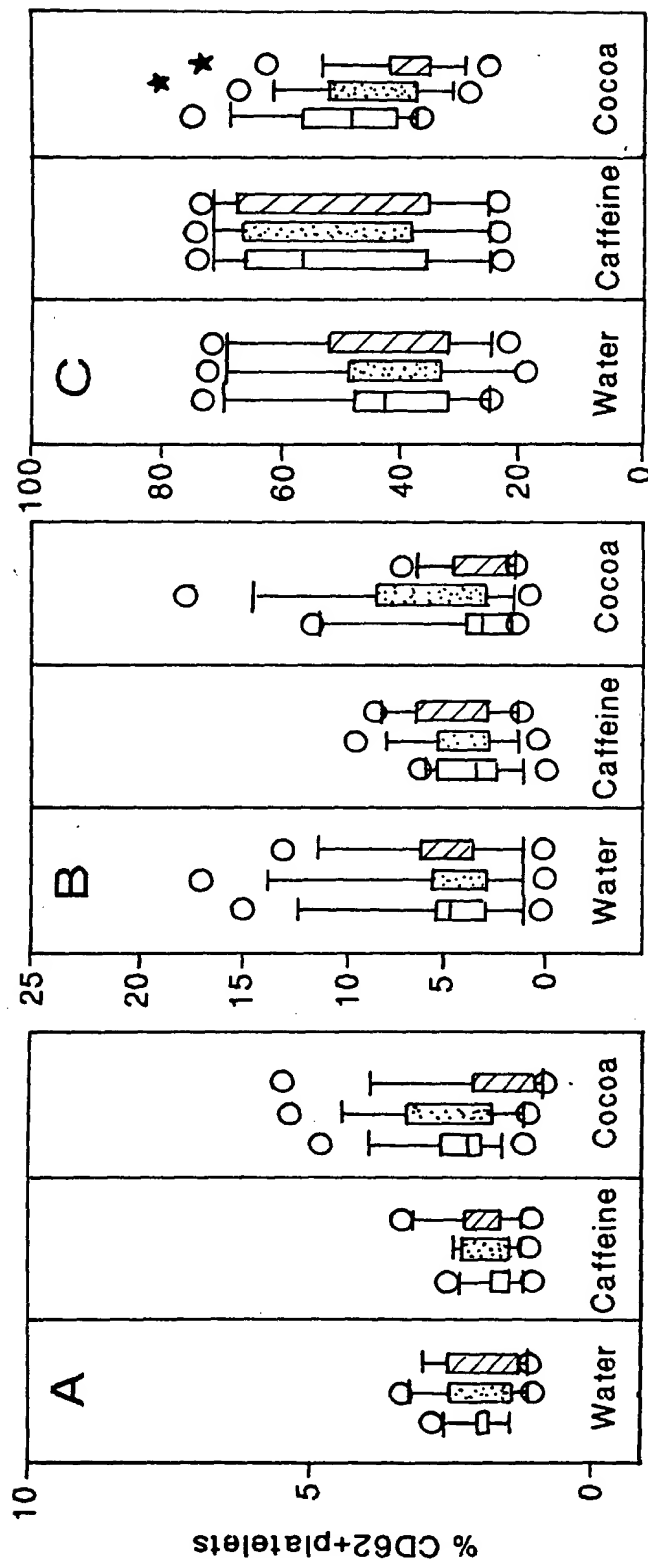
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FIG.21



Effect of cocoa beverage consumption on platelet surface expression of activated GP11b-111a with and without stimulation with weak agonists. Platelet activation marker expression is presented as Tukey box plots at times zero (white boxes), 2 hours (light grey boxes), and 6 hours (dark grey boxes) post consumption of water, a caffeine-containing control beverage (caffeine) or a cocoa beverage (cocoa). (A) percentage of platelets expressing activated gp11b-111a (PAC1= platelets) without stimulation (B) after stimulation with epinephrine (20uM) or (C) with ADP (20uM). Activated GP11b-111a is expressed on the surface of activated platelets. Each box shows the 25-75th percentile, the horizontal bar in the box shows the median. The lines outside the box show the 10th and 90th percentile. Asterisks indicate $P < 0.05$ between zero time and 6 hour time points of each respective data set repeated measure ANOVA on ranks, Student-Newman-Keuls multiple comparison method, $n=10$ in each

FIG.22



Effect of cocoa beverage consumption on platelet surface expression of activated P-selection with and without stimulation with weak agonists. platelet activation marker expression presented as Tukey box plots at times zero (white boxes), 2 hours (light grey boxes) and 6 hours (dark grey boxes) post-consumption of water, a caffeine-containing control beverage (caffeine) or a cocoa beverage (cocoa). (A) Percentage of platelets expressing P-selection (CD62P+platelets) without stimulation, (P) after stimulation with epinephrine (20uM) or (C) with ADP (20uM). P-selection is expressed on the surface of activated platelets. Asterisks indicate $P < 0.05$ between zero time and 2 hours and between zero time and six

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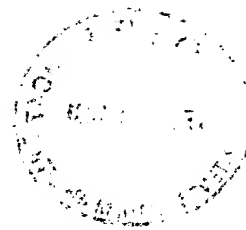
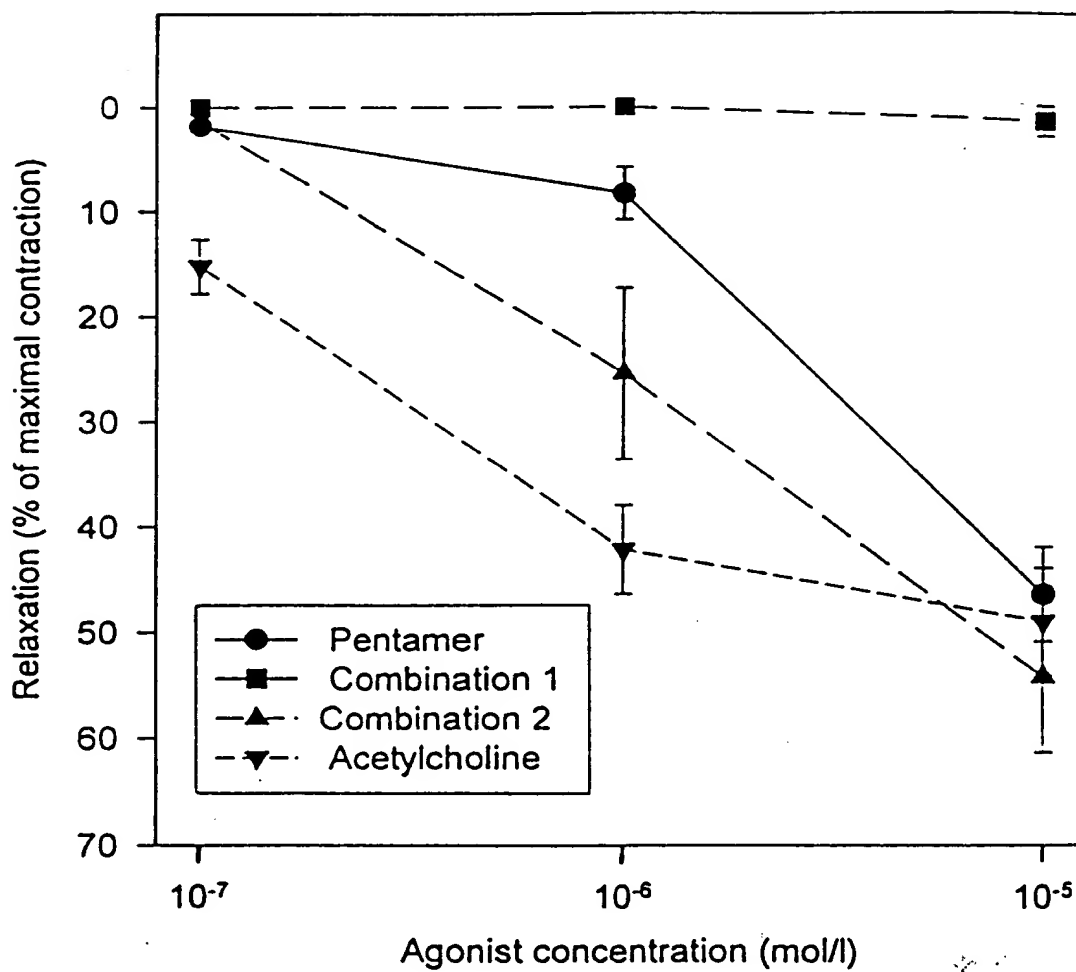


FIG.23



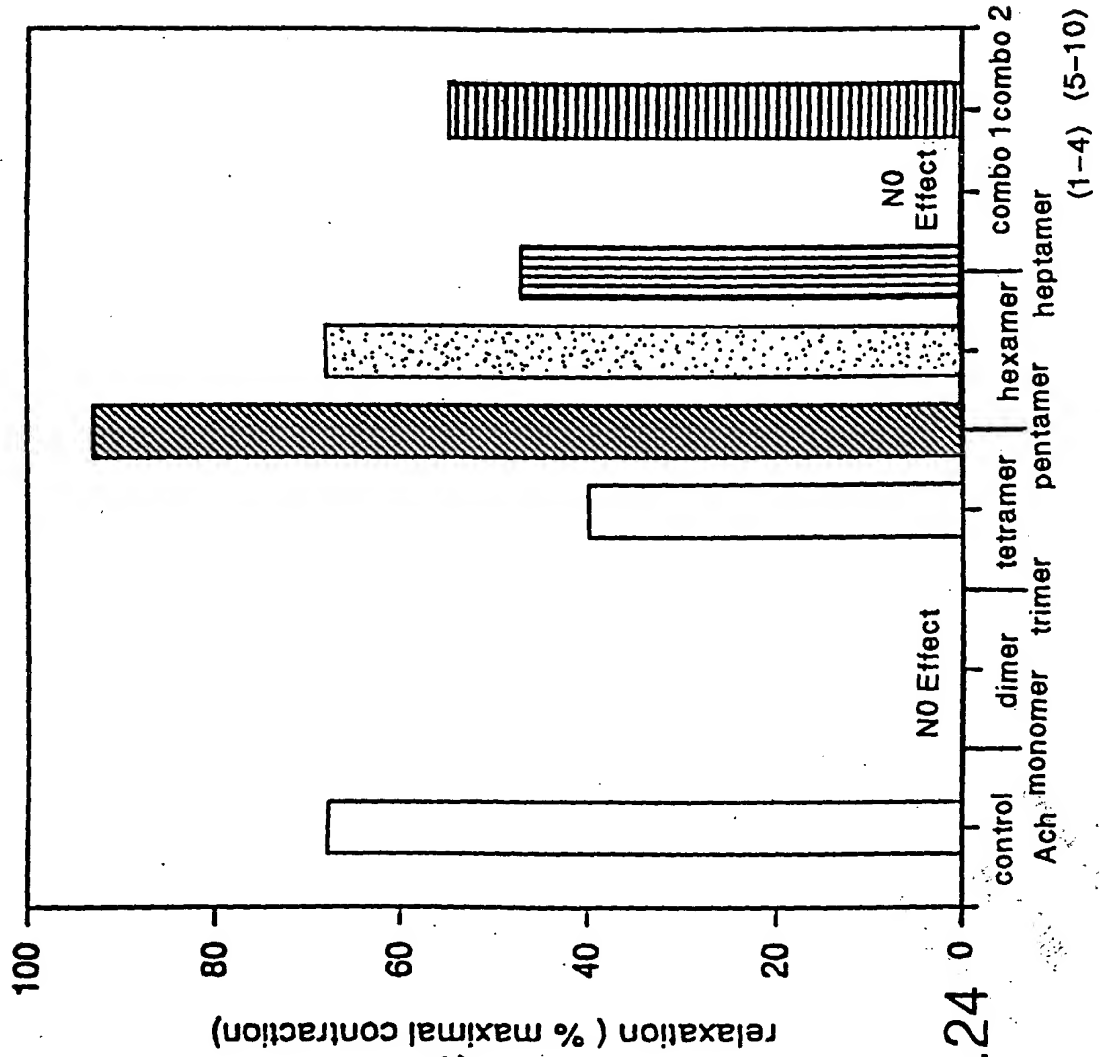


FIG.24

Single dose
10⁻⁵M